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9. The methods of statistical analysis should be described in detail sufficient that a knowledgeable reader could reproduce the analysis if the data were available.

**From* Methodologic Guidelines for Reports of Clinical Trials (Cancer Treat Rep 69:1-3, 1985).

Contents

Cancer Treatment Reports
Volume 70, Number 9
September 1986

EDITORIALS

1051 Low-Grade Non-Hodgkin's Lymphomas Revisited. **B. D. Cheson, R. E. Wittes, and M. A. Friedman.** National Cancer Institute, Bethesda, Maryland

1055 Follicular Lymphoma—Do No Harm. **S. E. Jones.** Baylor University Medical Center, Dallas, Texas

ORIGINAL ARTICLES

1059 Pharmacology and Toxicity of High-Dose Cytarabine by 72-Hour Continuous Infusion. **R. C. Donehower, J. E. Karp, and P. J. Burke.** The Johns Hopkins Oncology Center, Baltimore, Maryland

1067 Effects of Exercise on Bleomycin-Induced Pulmonary Toxicity in Mice. **D. W. Stone, E. A. Copelan, S. E. Weisbrode, and H. Rozmiarek.** The Ohio State University, Columbus

1073 Ineffectiveness of Levamisole in Prolonging Remission or Survival of Women Treated With Cyclophosphamide, Doxorubicin, and 5-Fluorouracil for Good-Risk Metastatic Breast Carcinoma: A Southeastern Cancer Study Group Trial. **J. T. Carpenter, Jr, R. V. Smalley, M. Raney, C. L. Vogel, and R. S. Weiner.** Southeastern Cancer Study Group

1081 Hyponatremia and Other Toxic Effects During a Phase I Trial of Recombinant Human Gamma Interferon and Vinblastine. **C. L. Bennett, N. J. Vogelzang, M. J. Ratain, and S. D. Reich.** University of Chicago Hospitals and Michael Reese Hospital and Medical Center, Illinois, and Biogen Research Corporation, Cambridge, Massachusetts

1085 Randomized Comparisons of Radiotherapy and Carmustine Versus Procarbazine Versus Dacarbazine for the Treatment of Malignant Gliomas Following Surgery: A Southwest Oncology Group Study. **H. J. Eyre, J. R. Eltringham, E. A. Gehan, F. S. Vogel, M. Al-Sarraf, R. W. Talley, J. J. Costanzi, J. W. Athens, N. Oishi, and W. S. Fletcher.** Southwest Oncology Group

1091 Trial of the Combination of Mitomycin, Vindesine, and Cisplatin in Patients With Advanced Non-Small Cell Lung Cancer. **M. G. Kris, R. J. Gralla, M. S. Wertheim, D. P. Kelsen, J. P. O'Connell, M. T. Burke, J. J. Fiore, I. R. Cibas, and R. T. Heelan.** Memorial Sloan-Kettering Cancer Center, Cornell University Medical College, New York, New York

1097 Phase II Trials of Cisplatin and Piperazinedione as Single Agents in the Treatment of Advanced or Recurrent Non-Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study. **J. T. Thigpen, J. A. Blessing, W. C. Fowler, Jr, and K. Hatch.** Gynecologic Oncology Group

1101 Extensive Non-Small Cell Lung Cancer Treated With Mitomycin, Cisplatin, and Vindesine (MiPE): A Southwest Oncology Group Study. **T. P. Miller, R. B. Vance, F. R. Ahmann, and S. R. Rodney.** Southwest Oncology Group

REVIEW ARTICLES

1105 Therapeutic Response in Phase I Trials of Antineoplastic Agents. **E. Estey, D. Hoth, R. Simon, S. Marsoni, B. Leyland-Jones, and R. Wittes.** National Cancer Institute, Bethesda, Maryland

1117 Association of Severe and Fatal Infections and Treatment With Pentostatin. **P. J. O'Dwyer, A. S. D. Spiers, and S. Marsoni.** National Cancer Institute, Bethesda, Maryland, and The Albany Medical College, New York

BRIEF REPORTS

1121 Treatment of Kaposi's Sarcoma in Acquired Immunodeficiency Syndrome With an Alternating Vincristine-Vinblastine Regimen. **L. Kaplan, D. Abrams, and P. Volberding.** University of California and San Francisco General Hospital

CLINICAL TRIALS SUMMARIES

1123 Phase II Study of Fludarabine Phosphate for the Treatment of Advanced Non-Small Cell Carcinoma of the Lung: A Southwest Oncology Group Study. **G. R. Weiss, J. Crowley, D. D. Von Hoff, S. A. Taylor, R. J. Belt, C. A. Coltman, Jr, H. E. Hynes, and J. H. Costanzi.** Southwest Oncology Group

1125 Phase II Trial of Mitoxantrone in Advanced Primary Liver Cancer: A Cancer and Leukemia Group B Study. **R. B. Davis, D. A. Van Echo, L. A. Leone, and E. S. Henderson.** Cancer and Leukemia Group B

1127 Phase II Clinical Trial of Diaziquone in the Treatment of Patients With Recurrent Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study. **R. E. Slayton, J. A. Blessing, F. B. Stehman, and J. Malfetano.** Gynecologic Oncology Group

1129 Phase II Study of Spirogermanium in Metastatic Prostate Cancer. **F. H. Dexeus, C. Logothetis, M. L. Samuels, and B. Hossan.** The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston

LETTERS

1131 "Some Thoughts on the Future of Clinical Trials in Cancer." **S. E. Salmon.** University of Arizona College of Medicine, Tucson

1133 "Some Thoughts on the Future of Clinical Trials in Cancer." **E. D. Crawford.** University of Colorado, Denver

1133 Testing Hypotheses in Clinical Trials: Experience of the National Cancer Institute of Canada Clinical Trials Group. **J. L. Pater, E. Eisenhauer, W. Shelley, and A. R. Willan.** National Cancer Institute of Canada, Queen's University, Kingston, Ontario

1136 "Some Thoughts on the Future of Clinical Trials in Cancer." **D. J. Higby.** Baystate Medical Center, Springfield, Massachusetts

1137 *Reply:* Clinical Trials. **R. E. Wittes, M. A. Friedman, and R. Simon.** National Cancer Institute, Bethesda, Maryland

1139 Chemosensitization of Lomustine by Misonidazole, Benznidazole, and RSU 1069. **P. Workman.** Medical Research Council Centre, Cambridge, England

1140 Linear and Exponential Interpolation. **Z. Guolong.** Henan Medical University, Zhengzhou, The People's Republic of China

1143 ANNOUNCEMENTS

EDITORIAL

Low-Grade Non-Hodgkin's Lymphomas Revisited[1]

Bruce D. Cheson,* Robert E. Wittes, and Michael A. Friedman[2]

The non-Hodgkin's lymphomas (NHLs) can be practically classified into the so-called low-grade NHLs (L-NHL), which include nodular and diffuse well-differentiated lymphocytic lymphoma (WDLL), nodular poorly differentiated lymphocytic lymphoma (NPDL), and nodular mixed lymphoma (NML), and the intermediate- and high-grade NHLs (I/H-NHL), which include nodular histiocytic lymphoma and the remaining diffuse histologies (1). The terms L-NHL and I/H-NHL reflect the tendency of these lymphomas to behave in relatively indolent or aggressive fashions, respectively, and, therefore, appear to have clinical relevance. There is also a striking difference in durability of the response of L-NHL and I/H-NHL to chemotherapy. Based on the aggregate experience at Stanford (2,3) and other published series (4,5), chemotherapy results in objective responses in the majority of patients with stage III-IV L-NHL, although cures are not observed. In contrast, combination chemotherapy cures many patients with advanced I/H-NHL (6).

The apparent incurability of patients with advanced-stage L-NHL has often led to deferral of treatment until clinical indications are manifest, at which point patients can then be treated with an orally administered alkylating agent. Such a conservative approach to patients with stage III-IV L-NHL has received additional support from two recent major cooperative group trials. The Cancer and Leukemia Group B (CALGB) randomized 220 patients with stages III-IV NPDL and NML to receive either daily oral cyclophosphamide (100 mg/m^2) or a combination of cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin (CAVPB) (7). Of 128 patients evaluable for response, the complete response (CR) rate (66%), median time to response (9 months), and the 3-year disease-free survival (66%) were identical for the two groups. The results are preliminary, and the follow-up period is too brief to detect any long-term differences. In a recent Eastern Cooperative Oncology Group (ECOG) study (8), patients with stage III and IV NPDL were randomized to receive cyclophosphamide and prednisone (n = 48); cyclophosphamide, vincristine, prednisone, and procarbazine (COPP) (n = 27); or carmustine, cyclophosphamide, vincristine, and prednisone (BCVP) (n = 53). CR rates were similar for the three arms at 54%, 56%, and 53%, respectively. Although disease-free survival was best for the COPP-treated patients, overall survival for the three groups was similar. These data suggest that conventional combination therapy is not better therapy for patients with L-NHL, since few patients with stage III-IV disease are cured with such treatment despite a moderate increase in drug-related toxic effects, particularly neutropenia, which are associated with the more aggressive regimens.

Is aggressive chemotherapy in advanced L-NHL worth pursuing? A number of recent observations should stimulate a reassessment of our approach. First, there are probably important differences in the natural history of subsets of L-NHL. For example, patients with NML appear to benefit from aggressive therapy. Longo et al (9) reported that 46 of 64 patients (72%) with stage III-IV NML achieved CR with C-MOPP (cyclophosphamide, vincristine, prednisone, and procarbazine); the median remission duration was > 6 years, although relapses were observed even after 8 years. Results with CVP (cyclophosphamide, vincristine, and prednisone) in patients with NML were similar to C-MOPP, with 58% achieving CR and 27% remaining in CR after 9 years of follow-up. For their patients with NPDL treated with CVP, however, the median duration of disease-free survival was only 2 years. Moreover, a plateau in survival was suggested from the NML data and was not apparent for NPDL. Unfortunately, data for C-MOPP treatment of NPDL were not available. While an earlier, retrospective study from ECOG (10) supported the use of aggressive chemotherapy in NML, this was not substantiated by a prospective randomized trial from

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the same group (11). Although discrepancies between the National Cancer Institute (NCI) and ECOG studies have been attributed to differences in dose and schedule of drugs (9), the differences in dose intensity between the two regimens are rather unimpressive. The NCI C-MOPP regimen includes cyclophosphamide (650 mg/m^2) and vincristine (1.4 mg/m^2) on Days 1 and 8, with prednisone (60 mg/m^2) on Days 1-14. The doses of these drugs in the ECOG COPP regimen are cyclophosphamide (600 mg/m^2) and vincristine (1.2 mg/m^2) on Days 1 and 8. Although the daily dose of prednisone is higher in COPP at 100 mg/m^2, it is administered only on Days 1-5. The dose of procarbazine was identical in both trials. It also seems unlikely that the disparity in the results of these two studies is related to differences in the interpretation of the pathologic material, since biopsy material from both groups of patients was reviewed by the same reference pathologist.

Since L-NHL tends to be very sensitive to even single-agent chemotherapy, it is puzzling that more durable responses cannot be achieved with combination chemotherapy. One possibility for the failure of multidrug therapy to cure patients is that the regimens which have been used are not sufficiently intensive. Recent experience with I/H-NHL provides indirect support for such a hypothesis. The development of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) represented an important advance in the treatment of patients with I/H-NHL. CRs were achieved in $\leq$ 58% of patients, with half of those being durable (cures) (6). While response rates for L-NHL were at least comparable, no plateau was apparent. A number of current regimens [M-BACOD (methotrexate, leucovorin, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone [12]); PROMACE/MOPP (doxorubicin, cyclophosphamide, methotrexate, prednisone, etoposide, mechlorethamine, vincristine, and procarbazine [13]); MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin [14]); and others [15-17])] incorporate high-dose multiagent therapy administered at frequent intervals in an attempt to improve on CHOP. The data with these regimens suggest that better results can be achieved with programs more complicated and aggressive than CHOP, with CR rates $\leq$ 84% and relapse-free survival rates often $>$ 70% (12-14,16). It is likely that at least one of these regimens will have substantially greater efficacy than CHOP in I/H-NHL.

Unfortunately, patients with L-NHL have rarely been treated with regimens more intensive than CHOP or M-BACOD (18). Data from an ongoing trial conducted at the NCI using the aggressive PROMACE/MOPP regimen with total lymphoid irradiation are too preliminary for comment. The decision to study intensive regimens in L-NHL systematically should not be influenced by prior experience with combinations such as CHOP, which would not be considered aggressive by contemporary standards. Whether one of the more intensive combinations would improve the quantity and/or quality of the response in unselected patients with L-NHL remains speculative, yet it is a question which is certainly worth asking.

A potential source of support for the curability of patients with L-NHL with aggressive chemotherapy could be provided by evidence of cures resulting from high-dose chemotherapy, with or without radiation therapy, requiring bone marrow transplantation. Unfortunately, however, most of the available data are for patients with I/H-NHL who are refractory to conventional-dose alkylator therapy yet may be cured with high doses of an alkylator requiring marrow support (19-22). Bone marrow transplantation has rarely been performed for patients with L-NHL. Only nine cases have been identified from the Seattle experience (F. Appelbaum, personal communication), a recent survey for the International Bone Marrow Transplant Registry (J. Armitage, personal communication), and published data (20). These patients have been treated at different stages of disease activity and with a variety of preparative regimens. The limited experience with transplantation in patients with L-NHL reflects the fact that patients with L-NHL tend to be older and to have marrow involvement. Moreover, since such patients are considered to have an "indolent" process, a transplant is rarely considered until the disease has transformed into I/H-NHL, at which time the results have been disappointing.

Since clinically meaningful dose-response relationships exist for I/H-NHL, we should attempt to delineate and, if possible, exploit dose-response relationships in patients with the more responsive L-NHL through the development of new, aggressive regimens. The construction of such regimens is made more feasible by the existence of active agents, some with minimal myelotoxicity, so as not to compromise the dosage and contribution of other active agents.

In fact, a number of new, active drugs have been introduced over the last few years which could be used to develop potentially curative regimens for L-NHL. Chemotherapy agents worth pursuing in combinations include mitoxantrone, *m*-AMSA, mitoguazone, and gallium nitrate. Of particular interest are two drugs with unique biologic properties, pentostatin (DCF) and the interferons (IFN). DCF is an adenosine deaminase inhibitor which is highly active in patients with hairy cell leukemia (23,24) and induces a substantial number of responses in various histologic and immunologic subtypes of NHL as well (25,26). DCF has central nervous system and renal toxicity but is relatively nonmyelotoxic. It could, therefore, be incorporated into combinations without requiring substantial dose reduction of other active agents. There are currently no clinical trials in which DCF is being evaluated in combination with other agents.

A number of published reports and ongoing clinical trials have established a role for IFN in the treatment of NHL (27-29). Foon et al (29), using a high dose of recombinant alpha-IFN (50×10^6 units/m^2 three times weekly for at least 3 months), induced responses in 54%

of patients with low-grade lymphomas, in 33% of patients with intermediate-grade lymphomas, and in 14% of patients with high-grade NHL, all of whom had received extensive previous treatment. Unfortunately, this dose is probably too toxic to combine with chemotherapy. Not only were systemic symptoms severe, but myelotoxicity was pronounced as well, although not dose-limiting in this setting.

Currently, a number of trials are being proposed to evaluate the activity of alpha-IFN in L-NHL in combination with either an alkylator, an alkylator plus prednisone, or a conventional multiagent regimen. To study the role of alpha-IFN in an induction regimen, the CALGB is planning to treat patients with advanced-stage L-NHL with daily oral cyclophosphamide with or without concomitant alpha-IFN. The Southwest Oncology Group has proposed a similar study in which a 5-day course of oral chlorambucil is administered once a month with or without alpha-IFN three times a week. The Northern California Oncology Group has taken a somewhat different approach in which patients are induced into CR with CVP and then are randomized to no further therapy or maintenance with alpha-IFN. The ECOG has recently completed a pilot phase II study of alpha-IFN in combination with a CHOP-like regimen (I-COPA; recombinant alpha-IFN, cyclophosphamide, doxorubicin, vincristine, and prednisone) (30) for patients with intermediate-grade histologies and has recently activated a phase III study in which patients will be randomized to receive alpha-IFN. Valuable group-wide experience with alpha-IFN will be gained from these studies, while more aggressive regimens incorporating alpha-IFN are being considered for the future.

It seems unlikely to us, however, that any of these combination regimens has a reasonable expectation for curing patients with L-NHL. Since each of the randomized studies will take several years to complete and even longer to detect any potential differences in survival between groups, it is important to approach the development of potentially curative regimens for L-NHL with less timidity. Pilot studies are needed now to provide information as to how best to incorporate new active agents into chemotherapy regimens of maximum intensity without requiring dose reduction of the other active agents. Still, such combinations would not be available for large-scale, cooperative-group testing for 1–2 years. For example, we are in immediate need of trials of current intensive chemotherapy regimens and aggressive alpha-IFN- and/or DCF-containing regimens to determine if cure of L-NHL is a realistic goal with our presently available agents.

Since patients with even stage III-IV L-NHL may have a protracted clinical course following conservative therapy, the concept of a "favorable," indolent disease has been widely accepted. As Portlock (1) has clearly pointed out, however, these diseases are in fact lethal. Acceptance of L-NHL as incurable is clearly counterproductive. What may be adequate therapy for clinical practice is not necessarily optimal clinical investigation. Clinical trial organizations that are not willing to attempt to innovate in difficult areas such as L-NHL are failing an essential aspect of their mission. The large body of evidence which fails to demonstrate any advantage for combination therapy only serves to reinforce the need for new approaches to the management of these patients. Future strategies for the treatment of L-NHL should be approached with an open mind and a consideration of the continual progress in our understanding of the biology of NHL.

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EDITORIAL

Follicular Lymphoma—Do No Harm[1]

Stephen E. Jones[2,*]

In the paper by Cheson et al in this issue (1), the authors have challenged us to renew our efforts to cure low-grade lymphomas. They argue that newer, more intensive regimens which have been developed for high-grade lymphomas should be evaluated in follicular lymphoma to conceivably alter the natural history of these lymphomas and that new regimens with investigational agents such as pentostatin, gallium, etc, might be highly effective against these neoplasms. This, indeed, is a bold challenge. Therefore, we should first review what we know about low-grade lymphomas.

Clinical Features and Natural History of Follicular Small Cleaved Cell (FSC) Lymphoma

In the working formulation, low-grade lymphomas include three histologic entities: diffuse small cell lymphoma (a cousin of common chronic lymphocytic leukemia), FSC lymphoma, and follicular mixed small and large cell (FM) lymphoma (2). All of these are B-cell neoplasms. The first lymphoma is usually easily distinguished from the two follicular lymphomas, although occasionally a pseudo-follicular pattern is observed. Of the two follicular lymphomas, the small-cleaved cell type is the prototype for an indolent lymphoma. FM lymphoma is a distinct entity, but its definition on morphologic grounds can be difficult, even for experienced hematopathologists (3). Clinically, FM lymphoma may have different features than FSC lymphoma: less initial bone marrow involvement; more likelihood of extranodal involvement; higher rates of transformation to large cell lymphoma; and perhaps a different pattern of response duration to chemotherapy, although this latter point remains controversial (4,5). Thus, when we discuss therapy for follicular lymphoma, we are emphasizing the treatment of FSC lymphoma and to a lesser extent the treatment of FM lymphoma.

Before discussing therapy it is important to review what we know about this disease. FSC lymphoma is a systemic disease from its outset, with 90% of patients manifesting easily detectable stage III or IV disease. During staging, the harder one looks for disease, the more one finds; bone marrow, spleen, liver, and mesenteric nodes are commonly involved (6,7). Careful examination of the peripheral blood often reveals lymphoma cells (7) and immunologic assessment of the peripheral blood reveals a high incidence of occult involvement (8), confirming the systemic nature of this disease. Under the microscope, mitoses are rare among the malignant cells, and nodules of tumor cells are surrounded by immunologically normal and benign-appearing lymphocytes. Over time the follicular pattern may be lost, more large cell may appear, and mitoses are more evident. Some of these lymphomas complete the transformation to a diffuse large cell or high-grade lymphoma.

At presentation, most patients with follicular lymphoma are asymptomatic, and some provide histories of lymphadenopathy which waxes and wanes. Spontaneous regressions are well-documented (9). The median age of patients is between 50 and 60 years old, with a sizable fraction of patients > 60 years of age. With treatment, most patients achieve remission (often complete), but these have not proved to be durable. With re-treatment, most patients again often respond. Over time, remissions become shorter and the rate of response lower, although the average time between treatments in a recent series was 33 months (10). Although these neoplasms are regarded as "indolent," they are indeed fatal. At autopsy as many as two-thirds of cases retain a follicular pattern of involvement. In a series from Stanford treated during the 1960s, the median survival of all patients with FSC lymphoma was 7.5 years (11). In a more recent series from London, the median survival was 9 years (10). Although this is a fatal disease, many patients survive for long periods of time and enjoy a good quality of life free of symptoms of the disease. This latter fact must be kept in mind when balancing side effects from treatment.

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TABLE 1.—Treatments that have been extensively evaluated in follicular lymphoma

Chemotherapy
Single-agent chemotherapy
Combinations of agents without doxorubicin (eg, CVP, CP, MOPP, COPP, BCOP, etc)*
Doxorubicin-based combination chemotherapy (eg, CHOP, CHOP-bleomycin, M-BACOD, etc)†
Radiotherapy
Involved- or extended-field
Total-nodal irradiation
Whole-body irradiation
Combined modality therapy

*CP = cyclophosphamide and prednisone; COPP = cyclophosphamide, vincristine, procarbazine, and prednisone; and BCOP = carmustine, cyclophosphamide, vincristine, and prednisone.

†M-BACOD = high-dose methotrexate, leucovorin, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone.

What Are the Results of Treatment for FSC Lymphoma?

The current approach to patients of deferring initial therapy until the disease progresses or symptoms develop (6) has evolved over time and is a direct consequence of considerable clinical research in the last 2 decades. In table 1, I have listed, in general terms, the most extensively studied therapeutic approaches to follicular lymphoma.

Although radiotherapy is not widely used for this disease, there are still those who advocate radiotherapy for follicular lymphoma (12–14). Occasionally, staging laparotomy is recommended prior to radiotherapy with curative intent. Radiotherapy techniques have been modified for follicular lymphoma, since it is necessary to treat the whole abdomen and all major lymph node areas because this is a systemic disease. If follicular lymphoma is a curable disease, radiotherapy should be curative, particularly for patients with localized disease. However, most reports on radiotherapy involve small numbers of highly selected patients, and when relapse patterns are critically reviewed there is no compelling evidence to support the view that radiotherapy is curative for FSC lymphoma (12–15). Indeed, a pattern of continued late relapse is observed.

Similarly, when systemic radiotherapy (total-body irradiation)—a more logical approach based on the systemic nature of the disease—is employed, there is still no evidence of curability (16–18). Even when radiotherapy is combined with chemotherapy the same results are achieved, but with more toxicity (19,20). Finally, there are no controlled randomized prospective trials which demonstrate that radiotherapy in any form cures FSC lymphoma or improves survival over any other form of initial therapy.

Chemotherapy, as it has been employed to date, usually produces high response rates (up to 80% CRs), but these have not proven to be durable, with 15%–25% of patients continuing to relapse each year after therapy, producing median CR durations of about 2 years for most series. Higher CR rates have been demonstrated for combination therapy [eg, CVP (cyclophosphamide, vincristine, and prednisone or prednisolone); CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone); and C-MOPP (cyclophosphamide, mechlorethamine, vincristine, procarbazine, and prednisone)] than for single agents (eg, chlorambucil), but no prospective randomized trial has yet demonstrated any survival advantage for combination therapy (5,6,18–20). Regimens with curative potential for large cell lymphoma such as CHOP have been thoroughly evaluated in follicular lymphoma and found to produce high CR rates, but not durable responses for FSC lymphoma (21–23). Unfortunately, despite the premise that more aggressive treatment might affect the natural history of follicular lymphoma, controlled trials utilizing more intense regimens have never been demonstrated to be of more benefit in prolonging CR duration or survival than less intensive programs (19,21–23). This is the lesson we have learned from clinical research of the 1970s.

What Is the Possibility That Newer Drug Programs Will Cure Follicular Lymphoma?

As Cheson et al (1) point out, this question is a viable research issue. Table 2 shows some of the newer regimens which are cited as superior to CHOP or its variants for the treatment of high-grade lymphoma. All of these regimens have been tested in single-institution uncontrolled pilot studies, but have produced high CR rates and durable CRs in 75%–80% of the patients who achieve CR (24–29). All regimens are associated with considerable toxicity and even treatment-related mortality as high as 10%. These pilot series vary greatly in the clinical features of patients under study. Some of these features are of profound prognostic significance, such as stage and age (30,31). Seemingly, these new regimens appear more active than CHOP, but only now are randomized, prospective, controlled trials under way for patients with high-grade lymphomas to prove the superiority of these programs over less toxic standard programs such as CHOP. Moreover, one of the allegedly "superior" regimens in table 2 has already been tested

TABLE 2.—Newer dose-intensive lymphoma regimens*

Acronym	Ref No.
M-BACOD	24
m-BACOD	25
ProMACE-MOPP	26
ProMACE-CytaBOM	27
COP-BLAM	28
MACOP-B	29

*m-BACOD = moderate-dose methotrexate, leucovorin, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone; ProMACE-CytaBOM = cyclophosphamide, doxorubicin, etoposide, prednisone, cytarabine, bleomycin, vincristine, methotrexate, and leucovorin; COP-BLAM = cyclophosphamide, vincristine, prednisone, bleomycin, doxorubicin, and procarbazine; and MACOP-B = methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin.

in follicular lymphoma. In high-grade lymphomas M-BACOD produced a 72% CR rate (24), but in follicular lymphoma only 56% of patients achieved CR, and the familiar pattern of continued relapse was again observed (32). Toxicity was severe and treatment-related mortality of 4% was observed. Thus, there is no evidence that M-BACOD, one of the new more intense regimens (table 2), altered treatment outcome in follicular lymphoma compared to any of the programs shown in table 1. Whether other regimens in table 1 are superior to M-BACOD and therefore might have a different effect on outcome remains unknown.

If these newer regimens are to be evaluated in follicular lymphoma, it must be done cautiously. With the evidence to date that CHOP or M-BACOD does not cure FSC lymphoma, the likelihood that other regimens in table 2 will do so is remote. What is clear is that these programs are associated with considerable toxicity, including the real possibility of treatment-related mortality. That is a major trade-off for a neoplasm with a median survival of 7–9 years and often long periods of asymptomatic disease well-controlled by intermittently, relatively low toxicity therapy (eg, alkylating agents, CVP, etc). If one could prove that some of the regimens in table 2 are superior to CHOP for high-grade lymphomas, more investigators might be willing to entertain their evaluation in the more indolent lymphomas.

Are There Research Leads Worth Pursuing?

FM lymphoma is different from FSC lymphoma on clinical and morphologic grounds although even expert pathologists have difficulty in reproducibly defining FM (3). There are data, albeit conflicting, that some patients with FM lymphoma may have prolonged remissions with combination chemotherapy (4,5). Recently, Grogan et al (33) described immunologic phenotypes of FM lymphoma, one with surface immunoglobulin and the other without, a pattern commonly observed in B-cell large cell lymphoma. It is conceivable that immunotyping, flow cytometry, or even studies of gene rearrangement in follicular lymphoma may allow us to define "high-risk" follicular lymphoma which should be treated aggressively with curative intent and more indolent disease which should be managed expectantly with palliation as the goal (33–36).

In addition, new agent research must continue and new combinations need to be developed. Cheson et al (1) have outlined some of the other promising areas for clinical research in the follicular lymphomas. In my opinion, the follicular lymphomas are ideal for evaluation of biologic response modifiers, probably in conjunction with chemotherapy. In a large prospective study of bacillus Calmette-Guérin, we demonstrated improved survival of patients with follicular lymphoma treated with bacillus Calmette-Guérin (21). Furthermore, interferon has shown its greatest activity in follicular lymphoma (37). Interferon, although myelosuppressive, is being tested in combination with single alkylating agents like chlorambucil or with more aggressive combinations (38). Both approaches need to be evaluated, since no one knows the ideal way to combine chemotherapy with biologic response modifiers like interferon.

CONCLUSION

The follicular lymphomas remain a clinical and research dilemma. They respond well to all forms of therapy, but continue to recur. New research approaches are needed, but we must apply these prudently in low-grade lymphomas which are often associated with an indolent course. New advances in our biologic understanding may permit us to identify more aggressive forms of follicular lymphoma suitable for dose-intense treatment.

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Pharmacology and Toxicity of High-Dose Cytarabine by 72-Hour Continuous Infusion[1,2]

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Most studies using high-dose cytarabine (ara-c) for the therapy of acute leukemia have employed intermittent short infusions. In this study, we have evaluated the pharmacology and toxicity of high-dose ara-c by 72-hour continuous infusion. Plasma ara-c concentrations varied from 3.6 μM at the starting dose of 4 g/m²/72 hours to 22.6 μM at 18 g. Plasma clearance appeared to decrease progressively at doses > 10 g, suggesting that the route of elimination was saturable. CSF ara-c concentrations ranged from 1.2 μM at 4 g to 4.1 μM at 18 g; the ratio of CSF to plasma ara-c decreased progressively from 0.33 at 4 g to 0.18 at 18 g. The toxic effects were significant and included myelosuppression, nausea, and vomiting in all patients. No single dose-limiting toxicity was identified. Further dose escalation was precluded by combined organ system effects, which included hepatic, pulmonary, renal, and gastrointestinal toxic effects. Attempts to incorporate a 72-hour infusion of ara-c into a combination chemotherapy regimen should proceed cautiously with a starting dose of 6 g/m²/72 hours. [Cancer Treat Rep 70:1059-1065, 1986]

Cytarabine (ara-c) has been an important component of chemotherapy regimens for acute nonlymphocytic leukemias (ANLL) since its introduction into clinical trial in the late 1960's (1-4). The most commonly used clinical dosing schedules recently have utilized doses of ara-c in the range of 100-200 mg/m² every 12 hours, either by intermittent bolus injection or continuous infusion (5-8). These schedules have been based in large part on the preclinical studies with L1210 leukemia, which demonstrated that treatment with multiple smaller doses was superior to single large bolus injections (9,10). Since there are at least three clearly defined variables which may influence the therapeutic efficacy of this S phase-specific agent (extracellular drug concentration, duration of drug exposure, and the proliferative status of the tumor cell population), the optimum dose and schedule for the use of ara-c may not have been determined.

Currently, schedules of drug administration which utilize doses of ara-c far in excess of those used in conventional-dose induction regimens are under study in an attempt to improve the antileukemia effects of this drug. Although the use of high-dose ara-c dates back to the early years of its clinical application (3,11,12), most of the recent activity in this area has been prompted by the studies of Rudnick et al (13). These authors utilized doses of 3 g/m² administered as a short infusion every 12 hours for three to four doses. This study has provided the basic format for a large number of subsequent studies using high-dose ara-c (14-18). Several of these studies have provided encouraging results, even in patients with refractory or poor-risk leukemia.

The standard induction regimen for ANLL at The Johns Hopkins Oncology Center has been sequential therapy with ara-c and daunorubicin. This regimen includes daunorubicin at a dose of 45 mg/m² on Days 1, 2, and 3 and ara-c in two 72-hour infusions of 2 g/m², one on Days 1-3 and a second on Days 10-12, when the maximal regrowth of residual leukemia has been predicted to occur. This schedule of drug administration is based on the observations that the initial cytotoxic drug(s) in a sequence can stimulate regrowth of residual tumor and enhance sensitivity to cell cycle active agents, such as ara-c, and that the timing of this enhancement is predictable (19-21). This approach has resulted in an encouraging improvement in the duration of unmaintained complete remissions in adult leukemia patients (20-22). In the Lewis × brown Norway F_1 hybrid rats bearing brown Norway myelocytic leukemia, increasing initial doses of ara-c produced graded increments of a

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humoral stimulatory activity and subsequent proliferation of the residual tumor (23). As an initial step in evaluating the feasibility and efficacy of higher clinical doses of ara-c by 72-hour infusion in timed sequential therapy, and to evaluate an alternative high-dose ara-c regimen to that which has been extensively studied by others, this study was undertaken. The purposes of the study were to determine the maximum tolerated dose of ara-c that could be given by 72-hour continuous infusion, to characterize the toxicity, to quantitate the ara-c concentrations achieved in plasma and CSF during the course of these infusions, and to accumulate preliminary evidence for the therapeutic efficacy of higher doses given in this schedule.

MATERIALS AND METHODS

Patient Selection, Evaluation, and Supportive Care

Patients eligible for this trial had either ANLL or acute lymphocytic leukemia (ALL) that was refractory to standard forms of therapy, had acute leukemia felt to be secondary to treatment for a prior malignancy, or were felt to be poor candidates for timed sequential therapy because of age ($\geq$ 55 years) or other risk factors. All patients were ambulatory and had no major organ system dysfunction at the time of entry. Informed consent approved by the Joint Committee for Clinical Investigation of The Johns Hopkins University School of Medicine was obtained prior to therapy.

Pretreatment evaluation consisted of physical examination, routine hemogram, chemistry studies, chest x-ray, routine spirometry, and bone marrow aspirate and biopsy. Physical examination, hematology and chemistry studies, and spirometry were repeated on a regular basis throughout the course of therapy. Blood samples for measurement of plasma ara-c concentration were obtained at 12–24-hour intervals during the course of the drug infusions. A patient's bone marrow was first evaluated for response to therapy on Day 10. If an aspirate contained leukemic cells, it was considered to have had no response; absence of leukemia was considered a complete tumor clearance (CTC). Complete remission (CR) was defined by Acute Leukemia Group B criteria (1). Bone marrow examinations were repeated on Days 10, 16, 26, and 36. Lumbar punctures were performed during Day 3 of the ara-c infusion for determination of ara-c concentrations. Other studies were performed as clinically indicated. The toxic effects encountered during the course of the study were graded according to the toxicity criteria of the Eastern Cooperative Oncology Group (ECOG) (24).

The supportive care provided these patients was standard for patients undergoing intensive chemotherapy expected to result in prolonged pancytopenias, except that all patients received total parenteral alimentation and were given nothing by mouth except necessary medication. Careful monitoring of body weight and a gradual forced diuresis during the course of therapy was also employed (25). The starting dose for this study was 4 g/m^2/72 hours, and further escalations can be seen accompanying the data in table 1.

Assay of Ara-c Concentrations

Plasma and CSF concentrations of ara-c and uracil arabinoside (ara-u) were measured using a reverse-phase high-performance liquid chromatographic (HPLC) method. The chromatographic conditions included a mobile phase of 0.01 M KH_2PO_4 (pH 3.5) with 10% methanol, an M6000A HPLC pump, U6K injector, and C18 Radial-Pak liquid chromatography cartridge in an RCM-100 radial compression module (all from Waters Associates, Milford, MA). The flow rate was 1.5 ml/minute. The effluent was monitored for UV absorbance at 280 nm with a model 450 variable wavelength absorbance detector (Waters Associates, Milford, MA). Peak height was used for quantitation. Blood and CSF were collected in heparinized tubes containing 50 μg of tetrahydrouridine, and plasma was removed promptly from whole blood by centrifugation. Plasma and CSF were kept at −40°C until they were analyzed. Radiolabeled ara-c (approximately 10,000 dpm of [5,6-^{3}H]ara-c with a specific activity of 18 Ci/mmol) was added to plasma as an internal standard (Moravek Biochemicals, Inc, Brea,

TABLE 1.—Ara-c concentrations during infusions

	Plasma					CSF		
Dose (g/m^2)	No. of patients	Mean ara-c, μM (range)*	Mean ara-u, μM (range)*	Ara-u/ara-c†	Mean ara-c clearance, ml/min/m^2 (range)	No. of patients	Mean ara-c, μM (range)‡	CSF/plasma
2	7	1.9 (0.5–4.5)	20.9 (7.0–39.0)	6.0–14.0	1003 (475–3800)	5	0.8 (0.5–1.5)	0.42
4	2	3.6 (2.2,5.0)	25.5 (22.0,29.0)	4.5–12.8	1056 (760–1727)	2	1.2 (0.9–1.7)	0.33
6	3	5.1 (3.9–6.4)	62.5 (36.0–87.0)	5.6–17.3	1118 (890–1462)	3	1.2 (0.7–1.8)	0.23
10	4	9.6 (5.3–19)	56.0 (42.0–92.0)	3.4–9.6	989 (500–1792)	3	2.9 (1.8–4.1)	0.30
14	4	16.3 (4.8–22)	90.0 (36–120)	4.0–7.5	816 (604–2770)	4	3.6 (2.6–5.4)	0.22
18	14	22.6 (14.0–71)	150 (76–149)	2.1–6.8	757 (240–1221)	8	4.1 (2.2–5.6)	0.18
24	1	41.0	102	2.5	557	—	—	—

*Samples were drawn every 12–24 hrs during infusion.
†Range of values for this ratio observed in treated patients.
‡CSF obtained on Day 3 of infusion by lumbar puncture.

CA). This amount of labeled drug was below the limit of sensitivity of the absorbance detection. These aliquots of plasma (100 μl) were then treated sequentially with an equal volume of 15% $ZnSO_4$ and 0.3 M $Ba(OH)_2$ in microcentrifuge tubes. Following final centrifugation at 1000 × *g*, a clear, protein-free supernate resulted that could be injected for analysis. CSF samples were injected directly. Recovery of ara-c with this method was 65% ± 13% ($n = 6$).

This assay has a practical limit of sensitivity for ara-c of 0.5 μM (50 pmol in 100-μl sample), and the standard curve is linear from that concentration up to at least 1 mM (0.1 μmol in 100-μl sample). Coefficient of variation for the assay is 12% at the low concentrations and < 5% at the highest concentrations. The limit of sensitivity for ara-u is 0.2 μM.

Mean concentrations of ara-c and ara-u for each individual patient were calculated using the number of samples available during the infusion, usually four to six. These values were then used to calculate a mean for the group at each dose level.

RESULTS

Patient Characteristics

A total of 28 patients were entered on study. The median age of these patients was 48 years (range, 19–75). Twenty-four patients had poor-risk ANLL and four had refractory adult ALL. Seven newly diagnosed patients who were treated with our standard regimen are included in the analysis of drug concentrations for comparative purposes. Of the 24 ANLL patients, eight were refractory to our standard timed sequential therapy (20–22). Thirteen patients were > 55 years of age and of these 13, five had therapy-related leukemias and three had acute myelofibrosis. Two additional patients presented with acute myelofibrosis and one other with a therapy-related leukemia.

Drug Concentrations Achieved During Infusions

Plasma ara-c concentrations achieved during these infusions at the various doses are shown in table 1. At 2 g/m², the standard dose of ara-c used in our timed sequential induction regimen, the mean plasma concentration of ara-c was 1.9 μM with a wide range observed among the seven patients studied. Plasma concentrations increased with each dose escalation up to a dose of 10 g/m²/72 hours. Doses above that level resulted in a proportionally larger increase in plasma level than administered dose. At all dosage levels, considerable variations of the plasma concentrations achieved were observed among patients. Plasma concentrations of ara-u also varied widely. The ratio of ara-u/ara-c ranged from 6.0 to 14.0 at 2 g/m²/72 hours and appeared to decrease at the higher doses. Ara-u concentrations exceeded ara-c by only 2.1–6.8 times at a dose of 18 g/m²/72 hours. Plasma clearances in the seven patients studied at the starting dose had a mean value of 1003 ml/min/m² with a wide range. Doses up to 10 g/m²/72 hours yielded very comparable values for plasma clearance. Above that dose the values obtained for clearance decreased progressively, suggesting that the major route of elimination was saturable. For any given patient, the variability in plasma ara-c concentration was usually less than ± 10% and in no case was greater than ± 25%.

Ara-c concentrations in the CSF reached a mean of 0.7 μM at 2 g/m²/72 hours increasing progressively to 4.1 μM at the 18-g/m²/72-hour dose. The ratio of ara-c concentrations in the CSF to those observed in plasma was 0.42 in the five patients studied at the starting dose and appeared to decrease with increasing dose, reaching 0.18 at 18 g/m²/72 hours. All but one patient treated at a dose > 10 g/m²/72 hours had a CSF concentration of ara-c in excess of 2 μM, a concentration which far exceeds that seen in plasma with other commonly used continuous-infusion schedules of drug administration.

Toxicity

The toxicity of this schedule of ara-c administration was formidable at the higher doses in this heavily pretreated group of patients, affecting several major organ systems. No arbitrary attempt was made to separate the toxic effects of this regimen from the effects of leukemia or the other supportive measures employed, and all events occurring during the treatment period are recorded.

Although myelosuppression was a consistent finding in this study even at the starting dose, the duration of peripheral blood granulocytopenia and thrombocytopenia and the contribution of ara-c are difficult to fully evaluate. This is the result of the heavily pretreated status of these patients, the refractoriness of their leukemia, and the fact that additional therapies were given if marrow hypoplasia was not achieved or if increasing blasts were noted on the serial marrows. Of the 13 patients who recovered granulocyte counts > 500/mm³, and who did not receive further therapy, the median time to recovery was 25 days (range, 17–115). The time to recovery was independent of dose in these patients.

The hepatic and renal toxicity encountered in this trial is shown in table 2. Grade 1 hepatic toxicity on the

TABLE 2.—Hepatic and renal toxicity of continuous-infusion ara-c*

Dose (g/m²/72 hrs)	*N*	Hepatic toxicity, ECOG grade—					Renal toxicity, ECOG grade—				
		0	1	2	3	4	0	1	2	3	4
4	2	0	0	1	1	0	2	0	0	0	0
6	3	1	0	2	0	0	2	1	0	0	0
10	3	0	1	1	1	0	0	1	1	0	1
14	4	1	0	1	2	0	1	1	2	0	0
18	14	1	4	6	3	0	4	2	6	2	0
24	1	0	0	0	1	0	0	0	0	0	1

*Values = No. of patients.

TABLE 3.—Pulmonary and GI toxicity of continuous-infusion ara-c*

Dose (g/m^2)	N	Pulmonary toxicity				GI toxicity			
		↓ FVC > 20% of baseline	↓ pO_2 > 20% of baseline	Infiltrates (chest x-ray)	Patients with > 1 abnormality†	Pain, distention, ileus	Melena	Sepsis (GI source)	Patients with > 1 abnormality†
2	7	0	0	0	0	0	0	0	0
4	2	0	0	0	0	0	0	0	0
6	3	0	0	0	0	1	2	1	2
10	4	2	2	2	2	3	3	0	3
14	4	1	1	1	2	1	0	1	2
18	14	6	6	5	8	3	5	2	7

*Values = No. of patients.
†> 1 of the abnormalities named here.

ECOG scale is considered to occur when serum transaminases (SGOT, SGPT), alkaline phosphatase, or bilirubin become elevated from 1.5 to 2 times the upper limit of normal. Grade 2 includes elevations from 2 to 5 times normal, and grade 3 includes elevations of > 5 times normal. Grade 4 is reserved for patients in hepatic coma. Hepatic toxicity was noted at the starting dose of 4 g/m^2/72 hours, where both patients developed elevations in their serum transaminases with no other changes. At doses of 6 and 10 g/m^2/72 hours, the toxicity continued to be suggestive principally of mild hepatocellular damage. At doses of 14 and 18 g/m^2, elevations of alkaline phosphatase and bilirubin began to consistently appear. The grade of toxicity indicated in table 2 for those doses was principally due to transaminase elevations, but ten of the 14 patients at the 18-g dose had elevations of alkaline phosphatase with a range of 1.5–10 times normal. Seven of the 14 patients had elevated total bilirubin with a mean of 2.5 mg/dl (range, 1.6–4.6). Those abnormalities typically appeared between Day 3 and Day 9 of a course of therapy, peaked within 1 or 2 days, and resolved over the succeeding 10–14 days.

Grade 1 nephrotoxicity for this study was considered to have occurred when serum creatinine was elevated in the range of 1.3–2.0 mg/dl; grade 2 includes elevations from 2.1 to 4.0 mg/dl; grade 3 includes elevations > 4.0 mg/dl; and grade 4 was defined by symptomatic uremia requiring dialysis. The degree of the toxicity encountered at each dose is shown in table 2. Grade 2 toxicity was first seen at 10 g/m^2/72 hours, and one patient at that dose developed renal failure requiring hemodialysis. This patient was receiving concomitant nephrotoxic antibiotics which may have contributed to this event. The frequency and severity of the toxicity increased at the 18-g dose, where nine of 14 patients had grade 2 or grade 3 toxicity. Abnormal renal function was typically noted on Day 2 to Day 12 and resolved over the next 14 days.

The lungs were also a site of toxicity with this schedule of administration, a finding that has not been frequently reported with other high-dose ara-c regimens. Significant pulmonary damage was detected with dose escalation of continuous-infusion ara-c (table 3). Toxicity, as measured by changes in forced vital capacity (FVC), oxygenation (pO_2), and chest x-ray, was first detected in two of the four patients receiving the 10 g/m^2 infusion. One of these patients had a 33% decrease in FVC by Day 2 of therapy, which was associated with progressive hypoxia and diffuse pulmonary infiltrates and required ventilatory support by Day 4. At the 18-g/m^2 dose, eight of the 14 patients had more than one measure of toxicity and four patients had detectable abnormalities of all three parameters. The mean decrease in FVC for the affected patients at that dose was 55% (range, 21%–75%), and the mean arterial pO_2 was 58 mm Hg (range, 43–65). Radiographic findings consisted of progressive diffuse interstitial infiltrates with associated pulmonary vascular congestion in the absence of changes in cardiac size or evidence for pericardial effusion. At 18 g/m^2, these abnormalities were first detected following the first 24 hours of the infusion in five patients and before the end of the 72-hour infusion in the remaining three patients. Evidence of this pulmonary compromise was reversible in six of eight patients with vigorous diuresis. In two patients, this pulmonary toxicity contributed significantly to their early death on this study.

Gastrointestinal (GI) toxicity, which increased with dose escalation, was detected in all patients. Mild to moderate nausea, vomiting, and diarrhea were experienced by all patients during the continuous infusions and resolved in all patients within 24–48 hours of the end of the infusion. Mucositis was not seen. Severe GI toxicity was encountered in the majority of patients receiving doses > 6 g/m^2. This was manifested by abdominal pain or ileus, GI bleeding, or gram-negative sepsis from a presumed GI source with organisms identified in their gut flora (table 3). At 18 g/m^2, eight of 14 patients had severe GI toxocity and seven of eight had more than one of these manifestations.

The incidence of combined organ system toxic effects is shown in table 4. Eight patients had both pulmonary and GI toxicity, seven had both pulmonary and renal, seven had both GI and renal, and six had significant combined renal, pulmonary, and GI toxic effects.

Central nervous system (CNS) toxicity was limited to somnolence during the infusions, which appeared to increase with dose. Obtundation and cerebellar toxicity

TABLE 4.—Combined organ system toxic effects*

Dose (g/m^2)	N	Pulmonary + GI	Pulmonary + renal	GI + renal	Pulmonary + renal + GI
2	7	0	0	0	0
4	2	0	0	0	0
6	3	0	0	0	0
10	4	1	1	2	1
14	4	2	1	1	1
18	14	5	5	4	4

*Values = No. of patients.

were not observed. Diffuse cutaneous erythema was seen in one patient at both 10 and 14 g, but was a universal finding at 18 g. Although this erythema was occasionally bullous, skin breakdown and compromised barrier function were not observed. Conjunctivitis was seen in all patients at doses > 10 g/m^2 unless steroid eye drops were used.

Tumor Response

The number of patients treated at each dose level who had CTC from their marrow on Day 10 or achieved a CR is shown in table 5. Only one of the seven previously untreated patients who were treated with our standard 2-g/m^2/72-hour infusion had CTC on Day 10. Similar findings were noted at the intermediate dosage levels of 4, 6, 10 and 14 g/m^2. However, at 18 g/m^2/72 hours, nine of 14 patients had CTC at Day 10; two patients included in this denominator did not have Day 10 marrows because of an early death. No patients achieved a CR with this regimen alone at doses < 10 g. Four of 12 patients at 18 g/m^2 entered brief CRs, without additional therapy. Two patients treated at 8 g/m^2 who had CTC at Day 10 received further chemotherapy before the clinical outcome from the protocol therapy could be evaluated and achieved a CR. They have not been included.

DISCUSSION

There has been renewed interest in exploring the use of higher doses of ara-c than those conventionally used in hematologic malignancies. Much of this has focused on the use of short infusions every 12 hours as described by Rudnick et al (13). This regimen, as usually administered, utilizes a dose of 3 g/m^2 as a 3-hour infusion and results in a plasma ara-c concentration of nearly 100 μM during the infusion (26). Prior to the next dose, the plasma ara-c concentration remains in the range of 1 μM, which is significantly higher than that achieved by conventional continuous-infusion schedules (5,7,8). In this paper, we describe and attempt to define the maximum tolerated dose of ara-c that can be given as a 72-hour continuous infusion, as an initial attempt to explore the use of higher ara-c doses in our timed sequential approach to the treatment of acute leukemia.

Using this schedule, the plasma ara-c concentrations achieved ranged from a mean 3.6 μM at our starting dose of 4 g/m^2/72 hours to > 20 μM at 18 g/m^2/72 hours. These values are tenfold to 100-fold higher than seen with conventional continuous-infusion schedules. Extremely wide variability was noted among patients treated at a single dosage level. Although in this initial study it was not possible to correlate the extent of toxicity or tumor clearance with plasma concentration of ara-c, some means of predicting plasma concentration in a given patient seems desirable. With methotrexate, this has been achieved by the use of a small test dose with pharmacokinetic analysis prior to the therapeutic infusion (27,28). We are currently exploring the usefulness of this approach to ara-c infusions.

Plasma clearance appeared to decrease with dose, suggesting that the major route of elimination might be saturable. However, the relatively small decreases in clearance observed and the fact that this occurred at plasma concentrations lower than the established Km for cytidine deaminase with ara-c as the substrate (29) leaves this area open to further investigation. Similarly, ara-u concentrations present in the plasma at the higher doses were well below its reported Ki for cytidine deaminase (22). It is not surprising that a drug whose plasma clearance depends heavily on an enzymatic mechanism would exhibit nonlinearity at high doses. Several authors have provided data that support this but it has not yet been unequivocally proven. CSF ara-c concentrations were > 1 μM at the starting dose and reached a mean of 4.1 μM at 18 g. There was no opportunity to judge the efficacy of the regimen against established CNS leukemia.

The toxicity encountered was significant and appeared to affect multiple organ systems. Two deaths were directly related to therapy. Myelosuppression was universal but not dose limiting. As the dose was increased the incidence of hepatic and renal toxicity increased as shown in table 2. Although the mechanism of these toxic effects is not known and the patients were receiving many other medications including nephrotoxic antibiotics, fluid restriction, and diuresis, it is certain that this represents, in part, ara-c toxicity. Abnormal liver function tests, including hyperbilirubinemia (chronologically related to ara-c administration), have been reported by several investigators, but the relationship to ara-c

TABLE 5.—Therapeutic outcome with continuous-infusion ara-c

Dose (g/m^2)	CTC*	CR*
2	1/7 (14)	—
4	0/2 (0)	0/2 (0)
6	0/3 (0)	0/3 (0)
10	1/4 (25)	2/4 (50)
14	1/4 (25)	1/4 (25)
18	9/14 (64)†	4/12 (33)‡

*Values = No. of patients with CTC or CR/No. treated (%).

†Denominator includes 2 patients who died prior to Day 10 and had no second marrow.

‡Excludes 2 patients with CTC who achieved CR but received treatment in addition to that specified by protocol.

has not been unequivocally established (6,11,30–32). Pulmonary toxicity was also seen at the higher doses in a pattern suggesting the noncardiogenic pulmonary edema seen more frequently in the timed sequential regimen (33). Although no single dose-limiting toxicity in all patients was identified, the constellation of hepatic, renal, and pulmonary dysfunction precluded further dose escalation.

The percentage of patients who had CTC from their marrow on Day 10 increased with the higher doses. Nine of 14 acute leukemia patients had CTC at 18 $g/m^2/72$ hours. Although this group of patients had admittedly a heterogeneous group of tumor cells, these data suggest a dose-response relationship for ara-c. The response rates recorded here are somewhat lower than those recorded in studies of alternate schedules of high-dose ara-c by other investigators. However, no firm conclusions should be drawn concerning relative efficacy because of the problems associated with comparisons between such studies.

This schedule for ara-c administration cannot presently be recommended as therapy for acute leukemia without further study. All patients on this study received total parenteral nutrition, placing their GI tract at rest and presumably minimizing the mucosal toxicity often seen with this drug. Attempts to incorporate a 72-hour ara-c infusion into a combination regimen should proceed cautiously if patients are taking food by mouth. With the gut at rest, a dose of 6–10 $g/m^2/72$ hours would appear to be a reasonable starting dose for combination studies. This dosage of ara-c can be expected to maintain a plasma concentration of ara-c between 5 and 10 μM. Plunkett and Liliemark (34) have recently shown that formation of the active metabolite, ara-CTP, by human leukemic blasts is saturated at concentrations from 5 to 10 μM. It is therefore possible, as they speculated, that ara-CTP formation can be maximized by continuous infusion at rates that approach this concentration. Drug levels which are higher than this and can not be metabolically converted to ara-CTP may only contribute to toxicity (34). We are currently attempting to cautiously introduce those higher doses of ara-c by 72-hour continuous infusion into timed sequential therapy.

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Effects of Exercise on Bleomycin-Induced Pulmonary Toxicity in Mice[1,2]

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NIH/Swiss mice were used to study the effects of exercise on bleomycin-induced pulmonary toxicity. After a 2-week exercise acclimation program the mice were treated with bleomycin sc twice a week and swim-exercised for 1 hour three times a week for 6 weeks. Based on higher mortality and significant weight loss in the exercise-drug-treated mice and a comparison of histological data, it is concluded that exercise exacerbates the toxicity of bleomycin. [Cancer Treat Rep 70:1067-1071, 1986]

Irreversible pulmonary toxicity is a frequent and potentially fatal side effect of the antitumor antibiotic bleomycin (1,2). The incidence of fatal bleomycin-induced pulmonary toxicity is about 1%–2%, while the incidence of nonfatal cases is 11%–23% (3). Factors which increase the risk of pulmonary toxicity with bleomycin administration are total dose, advanced age, prior pulmonary disease, other pulmonary-toxic drugs, and radiotherapy (4). Bleomycin-induced pulmonary toxicity is the dose-limiting factor in the administration of the drug and for this reason most chemotherapy protocols using bleomycin limit the total dose of bleomycin (4,5).

Efforts to reduce bleomycin-induced pulmonary toxicity have been extensive. Over 300 analogs of bleomycin, which differ only in their terminal moiety, have been evaluated for antitumor effectiveness and pulmonary toxicity in laboratory animals (2). The effect of chemical and physical agents on bleomycin-induced pulmonary toxicity has also been extensively studied. Ethanol and alpha-difluoromethylornithine (6), proline analogs (7), beta-aminopropionitrile (8), indomethacin (9), and radiation and oxygen (2,4,10) are among the many agents investigated.

Kanter et al (11) have shown that exercise significantly reduces the cardiotoxicity of doxorubicin in a mouse model. The mechanism by which exercise reduced doxorubicin-induced cardiotoxicity is unknown, but may be due to an increase of enzymes which combat free-radical damage (11). Since bleomycin is thought to react with molecular oxygen to generate superoxide and hydroxyl free radicals (4), it seemed conceivable that exercise could also decrease the toxic pulmonary effects of bleomycin. This study investigated the effects of exercise (swim-training) on bleomycin-induced pulmonary toxicity in a mouse model using a parenteral route and biweekly schedule of administration of the drug (4,12).

MATERIALS AND METHODS

Animals.—The mouse was chosen as an animal model for this study because it has been documented to develop bleomycin-induced pulmonary toxicity at 6–8 weeks following twice-weekly sc bleomycin injections (13), the disease produced is morphologically similar to the disease state seen in man (4), and it is able to easily adapt to exercise (11,14). Male NIH/Swiss albino mice [Hsd: (NIH)-(S)BR], Harlan Sprague-Dawley Inc, Indianapolis, IN), weighing 20–25 g on arrival, were used in the study.

Husbandry.—The animals were maintained in an accredited facility (American Association for Accreditation of Laboratory Animal Care); housed in polypropylene cages, six to 12 animals per cage, with corn cob bedding (Bed-O' Cobs, The Andersons Company, Maumee, OH); fed ad libitum (R. M. H. 3000, Agway Inc, Syracuse, NY); and maintained at 72°F ± 2°F and 40%–60% relative humidity, with a light cycle of 12 hours on and 12 hours off (6 AM on/6 PM off). The cages and bedding were changed twice each week. The animals were allowed to acclimate for 5 days prior to starting the study. The mice were exercised or weighed and injected starting at 5 PM each day to eliminate any diurnal variation.

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Exercise regimen.—On arrival the animals were randomly assigned into four groups: *Group 1.*—no exercise-no drug ($n = 10$); *Group 2.*—no exercise-drug ($n = 9$); *Group 3.*—exercise-no drug ($n = 11$); and *Group 4.*—exercise-drug ($n = 11$). Swimming was chosen as the method of exercise because swim training produces more consistent exercise intensity levels than does treadmill running, which requires frequent prompting to keep the animal running (15), and swimming exercise does not affect lung blood volume, lung weight, or body weight (16). Prior to starting bleomycin treatment, the animals in the exercise groups (Nos. 3 and 4) were acclimated to exercise by swimming them in water in a galvanized metal container 36 cm high × 70 cm wide on Mondays, Wednesdays, and Fridays. Starting at 15 minutes, the duration of swimming was increased in 15-minute increments up to 1 hour over a 2-week period (six sessions). After the 2-week acclimation program the animals in the exercise groups were swim-exercised for 1 hour every Monday, Wednesday, and Friday for 6 weeks (17 additional sessions, 23 sessions total). A three times per week exercise program was chosen because it is similar to the exercise patterns for normal and rehabilitative human programs (17,18). The following standards were followed for the swimming program: (*a*) water depth was maintained to at least 20 cm; (*b*) water temperature was maintained at 88°F to minimize temperature-induced stress (11,14); (*c*) all animals were continuously monitored and any animal which remained submerged for 15 seconds or longer was considered exhausted (14,16), immediately removed, and not exercised until the next scheduled session; and (*d*) both groups (Nos. 3 and 4) were exercised together. Those animals in the no-exercise groups (Nos. 1 and 2) were placed together in water to a depth of 3 cm at 88°F for 1 hour on Mondays, Wednesdays, and Fridays and received a similar acclimation program.

Drug administration.—Those animals in the drug-treated groups (Nos. 2 and 4) were weighed and administered 27.0 units/kg of bleomycin (Blenoxane, Bristol Laboratories, Syracuse, NY) sc twice each week (on Tuesdays and Thursdays), for a total of 11 treatments. Twice-weekly sc administration of bleomycin was chosen because it is similar to bleomycin administration in humans (4,12). The injection site was alternated in the left or right flank region. The bleomycin used (lot numbers: J3X05, M0X06, M0X07, and A2X06) was diluted (2.5 units/ml) with sterile physiological saline, so as to limit the total volume of drug administered to each mouse. Those animals not receiving bleomycin (Groups 1 and 3) were injected with sterile saline solution sc in a similar manner on each Tuesday and Thursday as a control.

Tissue collection.—The mice were killed 24 hours following the last bleomycin injection by an overdose of sodium pentobarbital administered ip and exsanguinated by transecting the abdominal aorta. The lungs were immediately removed en bloc and the tracheas cannulated with medical vinyl tubing, connected to a series of three-way stopcocks to a reservoir of 10% buffered Formalin, and maintained at 30 cm of water pressure for 24 hours as recommended by Dungworth et al (19). Following this fixation process the left lung was sectioned, embedded in paraffin, sectioned (5 μm) in the midsagittal anterior-posterior plane, and mounted on glass slides. These sections were then stained with hematoxylin and eosin (H & E) and Masson's trichrome stains. All slides were coded and randomized by an outside observer.

Morphometric analysis.—To standardize the quantification of the bleomycin-induced pulmonary toxicity the method as outlined by Sikic et al (13) was followed. Only those animals that survived until termination of the study were used for morphometric analysis. Three representative areas of the left lung lobe were selected for morphometric analysis: extreme anterior, extreme posterior, and right centrolateral. Care was taken to select only lung parenchyma consisting of alveoli and alveolar ducts and to avoid larger blood vessels, bronchioles, and bronchi. In each of these three areas the following parameters were measured: (*a*) The number of intra-alveolar macrophages and leukocytes per 0.05 m^2 was determined (magnification, × 430). (*b*) The total pulmonary cells (all nucleated) per 0.05 m^2 was calculated (magnification, × 430). (*c*) The mean alveolar wall thickness of ten alveolar walls using an ocular micrometer was measured (magnification, × 776). Only alveolar walls which appeared to be sectioned in a true perpendicular plane were measured. The width of ten alveolar walls was measured in each of the three areas so that the mean alveolar wall thickness for each mouse represented 30 measurements. (*d*) The mean percentage of consolidation of lung parenchyma was determined. At magnification × 100, an American Optical grid (type 3) containing 100 squares was overlaid in each of these three areas. Only those squares which contained at least 50% alveolar parenchyma were considered for evaluation. Any individual square which appeared ≥ 50% filled with cellular infiltrate, fluid infiltrate, and/or connective tissue was counted as consolidated. The values of each of the four parameters from the three sites was then averaged to determine the individual animal's composite score. Photomicrographs were taken on a Carl Zeiss photomicroscope model number 2, using Kodak Panatomic-X (ASA 25) film and processed in Kodak D-76 developer.

Statistics.—Only those mice that survived until the termination of the study were used for statistical analysis. The test of unequal variances for the morphological data was significant ($P < 0.05$) (20); therefore, the analysis used a nonparametric two-way layout with no interaction (21). The main effects used in the two-way layout were drug and exercise. The means of the biweekly body weights were computed for each group. The body weights displayed a normal distribution and the test for unequal variances was not significant ($P > 0.05$); therefore, these results were analyzed using parametric two-way analysis of variance. Pairwise comparisons were

investigated using the Scheffè pairwise multiple comparisons test (22). P values < 0.05 were considered significant.

RESULTS

Mortality.—Based on the study by Sikic et al (13), after the 2-week swimming acclimation, an 8-week biweekly treatment of bleomycin was planned (10 weeks total, including swimming). The study was terminated 2 weeks earlier than scheduled due to the high mortality in Group 4, where only six of the original 11 animals survived, and the need to maintain a statistically significant number of animals for morphometric analysis (fig 1). In the three remaining groups a total of two animals died, one each in Groups 1 and 2. No mortality occurred in Group 3. No deaths occurred as a direct result of swimming.

Body weight.—During the 2-week acclimation period prior to any bleomycin administration, there was no significant difference in body weight between any of the four groups (fig 2). There was no significant difference between the body weights of Groups 1 and 3 throughout the course of the study. After 2 weeks (Week 4) of bleomycin administration the drug-treated groups (Nos. 2 and 4) weighed significantly less than the no-drug-treated groups (Nos. 1 and 3). This difference remained throughout the duration of the study. By Week 8, Group 4 weighed significantly less than Group 2.

Morphometric analysis.—Microscopic examination of the lungs of both no-drug groups (Nos. 1 and 3) revealed normal histology. In contrast, both bleomycin-treated groups (Nos. 2 and 4) were qualitatively and quantitatively abnormal (fig 3). Qualitative changes seen in the alveolar macrophages consisted of a more abundant and foamy appearance to the cytoplasm compared with the macrophages in the no-drug groups. Fibroblasts were also more abundant in the bleomycin-treated mice. The

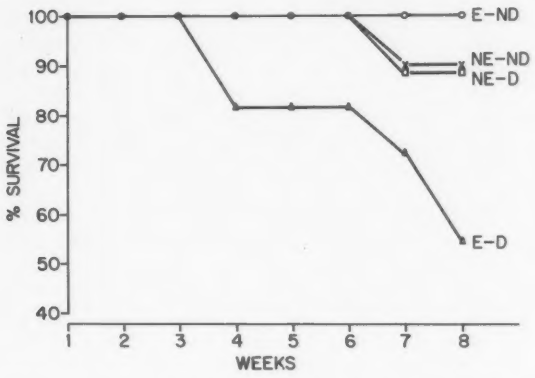

FIGURE 1.—% survival of mice in the 4 groups. Survival (%) is the No. of mice alive at each wk/total No. of mice at Week 1. Bleomycin treatment starts at Week 2. Group 1 (NE-ND; $n = 6$); Group 2 (NE-D; $n = 11$); Group 3 (E-ND; $n = 8$); and Group 4 (E-D; $n = 6$).

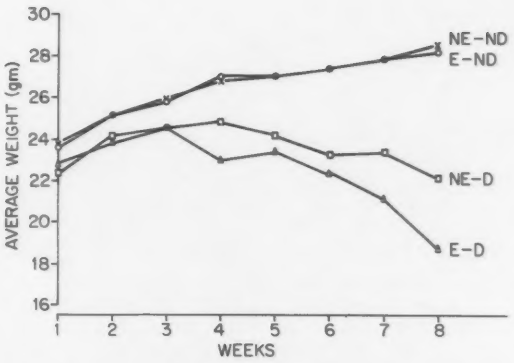

FIGURE 2.—Average body weights of the 4 groups. Bleomycin treatment starts at Week 2. Group 1 (NE-ND; $n = 6$); Group 2 (NE-D; $n = 11$); Group 3 (E-ND; $n = 8$); and Group 4 (E-D; $n = 6$).

lesions seen in the present study are similar to those reported previously (4,8,13,23) and confirm the value of the mouse in reproducing bleomycin-induced pulmonary toxicity. Only six animals from Group 1 were available for histopathology due to technical problems with lung inflation after the animals were killed. A minimum of $n = 6$ was considered adequate for statistical interpretation. Analysis of the four histological parameters measured is shown in tables 1 and 2.

Intra-alveolar macrophages.—Bleomycin caused a significant increase in the numbers of intra-alveolar macrophages ($P = 0.002$). The effect of exercise, while not significant, had a near significant effect on increasing the numbers of intra-alveolar macrophages ($P = 0.07$).

Total pulmonary cells.—Total pulmonary cells is the only parameter measured which showed a significant increase from exercise ($P = 0.027$). The effect of bleomycin also showed a significant increase in total pulmonary cells ($P = 0.0001$).

Alveolar wall thickness.—Bleomycin caused a significant increase in alveolar wall thickness ($P = 0.0001$), while exercise had no significant effect on alveolar wall thickness ($P = 0.30$).

Percent consolidation.—Bleomycin caused a significant increase ($P = 0.001$) in consolidation, while exercise had no effect ($P = 0.30$). Areas of consolidation in the bleomycin-treated mice were often focal and the transition from consolidated to nonconsolidated areas was often abrupt as reported previously in the literature (13).

DISCUSSION

The results of this study suggest that exercise exacerbates the toxicity of bleomycin. The mortality in Group 4 was markedly higher than in the other three groups. In addition, at the termination of the study, animals in Group 4 weighed significantly less than in the other three groups. The histologic data tend to support the

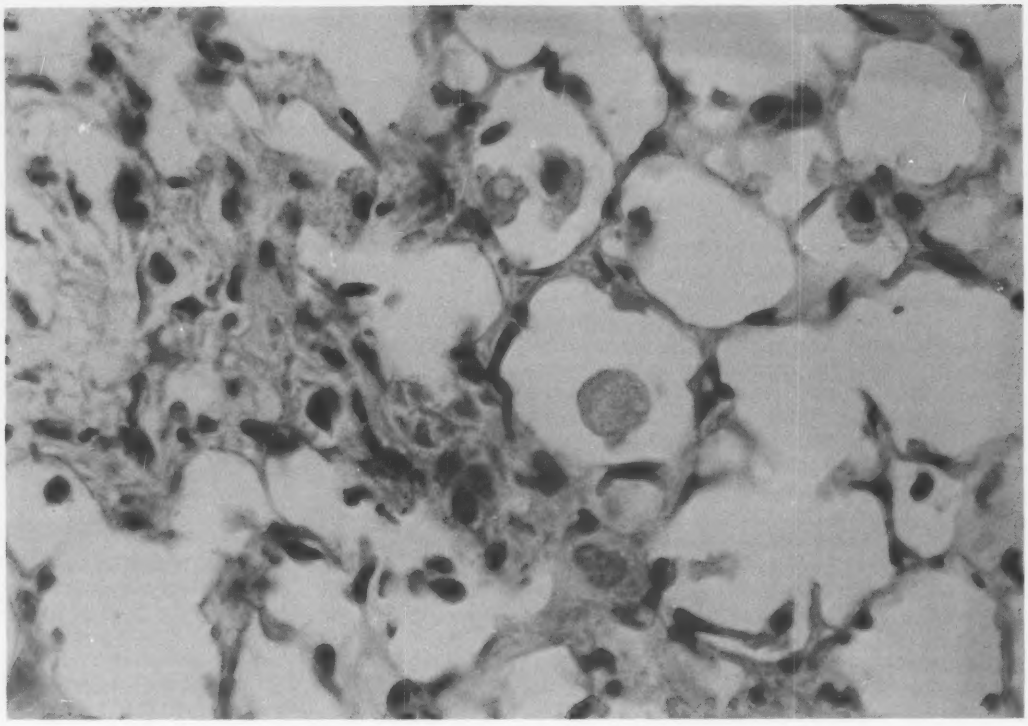

FIGURE 3.—Lung from a mouse in Group 4 showing areas of consolidation, increased Nos. of intra-alveolar macrophages, and thickened alveolar walls (H & E stain; original magnification, × 400).

greater toxicity of bleomycin with exercise, because Group 4 was consistently the highest in all parameters measured. In summary, all parameters measured (mortality, body weight, and histological data) were consistently more pronounced in Group 4 as compared to Group 2 or either of the two control groups.

The synergistic effect of radiation and bleomycin in exacerbating pulmonary toxicity has been well-documented (2,4,10). The production of oxygen free radicals is known to be associated with radiation damage (4,24). In addition, high concentrations of inspired oxygen have been shown to have a similar synergistic effect by increasing the incidence of bleomycin-induced pulmonary toxicity (2,4,10). The common denominator in both of these interactions appears to be the production of oxygen free radicals (4). It is possible that the deleterious effects of exercise seen in this study may be due to the marked increase in oxygen consumption. Alternating increases in hypoxia and hyperoxia that are seen with exercise result in the production of free radicals (11,25).

Sikic et al (13) reported a 35% mortality with biweekly sc administration of bleomycin at a dose of 20 mg/kg (approximately 35.7 units/kg) for 8 weeks in

TABLE 1.—Histological data: comparison of the effects of exercise and bleomycin on pulmonary toxicity*

Group No.	Intra-alveolar macrophages (cells/mm^2)	Total pulmonary cells (cells/mm^2)	Alveolar wall thickness (μm)	Consolidation (%)
1 (n = 6)	370 ± 181	2260 ± 403	1.33 ± 0.13	1.4 ± 1.9
3 (n = 11)	534 ± 242	2903 ± 1037	1.51 ± 0.24	0.9 ± 1.5
2 (n = 8)	991 ± 547	4202 ± 1986	2.20 ± 0.40	23.3 ± 28.6
4 (n = 6)	1570 ± 992	6676 ± 2278	2.28 ± 0.59	40.3 ± 30.9

*Values = mean ± SD.

TABLE 2.—Histological parameters: statistical analysis of the effect of exercise and bleomycin*

Histological parameter	Bleomycin	Exercise
Intra-alveolar macrophages	$P = 0.0002$†	$P = 0.07$
Total pulmonary cells	$P = 0.0001$†	$P = 0.03$†
Alveolar wall thickness	$P = 0.0001$†	$P = 0.30$
% consolidation	$P = 0.0001$†	$P = 0.30$

*Nonparametric 2-way layout using bleomycin and exercise as the main effects ($n = 31$).
†Significant ($P < 0.05$)

mice. In this study, using the same strain of mice, there was a 45% mortality in Group 4 mice that were exposed to a lower dose (27 units/kg) for a shorter duration (6 weeks). This same observation of the deleterious effect of exercise can be made for body weights, where Group 4 in this study had a greater loss in body weight at a lower dose in a shorter period of time than that seen in the Sikic et al (13) study.

One explanation for the differing effects of exercise on increasing the toxicity of bleomycin in this study and the decreased cardiotoxicity of doxorubicin seen in the study by Kanter et al (11) (besides the obvious differences in the chemotherapeutic agents themselves) may be the timing of the exercise in relationship to the start of the chemotherapy. In this study, exercised naive animals were given a 2-week conditioning program prior to starting the chemotherapeutic agent, while the study done by Kanter et al (11) conditioned the animals for 9 weeks prior to administration of any drug. This 9-week preconditioning could be a factor in explaining why both of these drugs responded as they did, since chronic aerobic exercise is known to increase the levels of many enzymes including those involved in the scavenging of free radicals (11,25).

There is a paucity of information available in the literature regarding the interaction of chemotherapy and exercise. The fact that exercise had any effect at all upon bleomycin-induced toxicity points to the need for more studies to delineate this interrelationship for this drug and for others.

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Ineffectiveness of Levamisole in Prolonging Remission or Survival of Women Treated With Cyclophosphamide, Doxorubicin, and 5-Fluorouracil for Good-Risk Metastatic Breast Carcinoma: A Southeastern Cancer Study Group Trial[1,2]

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A total of 97 women with good-risk metastatic breast cancer received therapy with cyclophosphamide, doxorubicin, and 5-FU; half of these patients were randomly allocated to receive levamisole, 2.5 mg/kg, 2 days of each week in addition to chemotherapy, while the other half received an identical placebo. Good-risk patients consisted of those with bone-only metastasis, or local chest wall recurrence with or without bone metastasis. No significant difference in response rate, duration of disease control, or survival was observed between the groups. No major toxicity was associated with levamisole. [Cancer Treat Rep 70:1073-1079, 1986]

In 1976, Rojas et al (1) reported that levamisole, an orally effective immunostimulant, produced prolongation of disease-free interval and survival when it was given to women with stage III breast cancer after radiotherapy to known areas of disease. They undertook the study because of data indicating that levamisole stimulated cell-mediated immune reactions (2). At that time, the capacity to develop delayed cutaneous hypersensitivity reactions had been correlated positively with survival and response to antineoplastic therapy in several studies (3,4). Trials in animals and man with nonspecific immunotherapy (BCG) had demonstrated prolongation of disease-free interval after patients were rendered free of disease by surgery or chemotherapy (5–8).

In 1978, the Southeastern Cancer Study Group (SEG) undertook a prospective randomized study of chemotherapy with or without levamisole in patients with good-risk patterns of metastatic breast cancer. Patients with good-risk patterns of metastasis (nodular local chest wall recurrence, or bone-only metastases) were selected for study because they had been shown to achieve higher response rates and longer survival in a previous study than those with poor-risk patterns (ie, lymphangitic pulmonary metastases, pleural effusion, or widespread metastases including hepatic) (9). Patients with nodular pulmonary metastases had an intermediate prognosis in that analysis. The primary objective of the study was to evaluate the effectiveness of levamisole in prolonging the duration of response and survival of patients who were treated with the most effective chemotherapy then available, which in the Group's experience at that time was a combination of cyclophosphamide, doxorubicin, and 5-FU (CAF) (10). It was thought that patients with a relatively low tumor burden, high probability of response to chemotherapy, and relatively long expected survival might have the best chance of benefit from levamisole. Good-risk patients, as described above, met these criteria and were used for this study. Patients were selected for study solely on the basis of the above clinical characteristics, not on the basis of any immunologic parameters.

PATIENTS AND METHODS

From August 15, 1978, through September 16, 1982, 105 patients were entered and randomized prospectively by telephone call to our Statistical Center to receive cytotoxic chemotherapy with CAF plus either levamisole or a placebo that was identical in appearance.

At the time of randomization, patients were stratified according to pattern of metastasis as pattern 1 (bone-

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TABLE 1.—Pretreatment characteristics of evaluable patients*

Pretreatment characteristic	CAF-levamisole	CAF-placebo
Median age (yrs)	58.5	54.9
Performance status (Karnofsky)		
Unknown	2	1
50–70	15	15
80–100	32	32
Pattern		
1	31	28
2	18	20
X-ray evidence of bone metastasis		
Yes	34	33
No	15	15
Previous hormonal therapy	49	48
With response	22	20

*Unless otherwise specified, values = No. of patients.

only metastasis) or pattern 2 (local skin or lymph node involvement with or without bone metastasis). To be eligible for randomization, patients were required to have metastatic breast cancer in one of the above two patterns and no previous treatment with cytotoxic drugs except as adjuvant therapy, which must have been completed > 6 months prior to entry. Patients whose tumors contained estrogen receptors were required to have received or refused prior hormonal therapy. *Pattern 1* was defined as metastasis only to bone as determined by bone scan or x-rays and physical examination. *Pattern 2* was defined as local anterior chest wall and/or supraclavicular or axillary nodal metastasis ipsilateral to the mastectomy site, with or without bone metastasis. Normal liver size on examination, normal liver function tests, negative liver scan, and no pulmonary or pleural metastasis on chest x-ray were required for all patients. Patients in either group were eligible only if they had an absolute granulocyte count of $\geq 1500/mm^3$. Prior to entering the study, all patients underwent physical examination, cbc, chemistry survey, chest x-ray, ECG, liver scan, bone scan, and x-rays of any areas of abnormal uptake on bone scan. The pretreatment characteristics of the two groups of patients are listed in table 1.

Patients received four courses of therapy as outlined in table 2, after which they were evaluated for toxicity and for response to therapy. The initial doses of therapy were set at 50% of full doses because previous SEG experience had indicated that patients with bone-only metastasis frequently experienced severe toxicity when CAF chemotherapy was started at full doses. In addition, preliminary analysis of the previous SEG study (SEG 253) had suggested that full- or half-dose CAF produced equal response rates. Those patients whose disease had responded to or stabilized on therapy were continued on the same treatment until disease progression occurred or until they received a total cumulative dose of 450 mg/m^2 of doxorubicin. Cytotoxic drugs (CAF) were then discontinued, but levamisole was continued until there was subsequent evidence of disease progression. Patients who experienced disease progression at any time after initiation of treatment were removed from study at that point.

The response criteria used were those of the SEG amended to conform to the chemotherapy subcommittee recommendations of the Breast Cancer Task Force (11). *Complete response (CR)* was defined as complete disappearance of all tumor for at least 1 month. *Partial response (PR)* was a $\geq 50\%$ (but not complete) shrinkage of tumor volume, determined by obtaining the sum(s) of the products of two perpendicular measurements of all measurable lesions, which persisted for at least 1 month. *Disease progression* was defined as a $\geq 25\%$ increase in tumor volume (as determined above) or the appearance of a new metastatic lesion. Patients whose disease neither responded nor progressed were classified as having *stable disease.* Those with bone-only metastases who improved clinically with improvement in performance status and disappearance of bone pain but whose bone scans or x-rays appeared stable or worse were classified as stable. Patients whose disease initially responded or stabilized were considered to have progressed when metastatic disease reappeared, new metastatic lesions appeared, or metastatic disease increased in size by 25% of tumor volume, compared to the smallest tumor volume observed on therapy.

Response duration was measured from the date the response was first observed to the time of the first sign of progression. The duration of disease control (time to progression) was measured from the date of the first treatment to the time of disease progression for all

TABLE 2.—Treatment regimen

Drug	Dose*	Route	Schedule
Cyclophosphamide	250 mg/m^2	Iv	Every 21 days
Doxorubicin	25 mg/m^2	Iv	Every 21 days
5-FU	250 mg/m^2	Iv	Every 21 days
Levamisole or placebo	2.5 mg/kg	Oral	Days 4, 5, 11, 12, 18, and 19 of each cycle

*Doses of CAF drugs were escalated to 375, 37.5, and 375 mg/m^2, respectively, on the second cycle of therapy and to 500, 50, and 500 mg/m^2, respectively, on the third and subsequent cycles if no toxicity (platelet count < $100,000/mm^3$ or absolute granulocyte count < $1500/mm^3$) was observed on weekly blood cell counts.

patients regardless of their response to therapy. All eligible patients were followed for survival and toxicity when data could be obtained.

Statistical Methods

Based on previous SEG experience (10), a CR plus PR plus stable response (nonprogression) rate of 95% was expected. The goal of the study was a $\geq 50\%$ increase in the median duration of disease control from the addition of levamisole to CAF. Based on a one-sided test of significance and an underlying exponential distribution, 76 patients were required for each arm, with a type I error of alpha = 0.05 and a type II error of beta = 0.20. Interim analyses of response rates and toxicity were performed every 6 months after the study opened. After approximately 4 years, the nonprogression rates were 25 of 37 patients (68%) for the CAF-levamisole arm and 24 of 34 patients (71%) for the CAF-placebo arm, which were well below the anticipated rate of 95%. At those response rates, 109 patients would be needed for each arm to complete the study. Since it did not appear feasible to accrue that many patients, the study was closed with 105 patients entered.

Survival, duration of remission curves, and duration of disease control curves were calculated with the Kaplan and Meier techniques (12) and compared for significance by the Gehan method (13). Other comparisons were made using chi-square statistics. The number of patients in this study is sufficient to detect a 50% increase in the median duration of remission and survival with alpha = 0.10 and beta = 0.25 using a one-sided test of significance.

RESULTS

A total of 105 patients were entered into this study and randomized, 97 of whom were eligible and formed the group who were further analyzed. Eight patients were not eligible because of pleural or pulmonary metastases (seven) or because of absence of bone or measurable soft tissue metastasis (one). Of the 97 eligible patients, there were ten for whom data were insufficient to evaluate response: one was lost to follow-up; three refused treatment after the initial dose of therapy; four did not have follow-up studies needed to evaluate response (such as bone x-rays), and for two, the investigator failed to provide needed data for evaluation.

Response rates were low, since most patients had bone-only metastases (pattern 1) where response evaluation is difficult. There were four patients with CRs, 11 with PRs, 46 with stable disease, and 26 with progressive disease. In none of these groups was there any significant difference between patients who did or did not receive levamisole. There was also no difference in the response rates of the two groups of patients with pattern 1 or pattern 2 disease, those who had or had not responded to prior hormonal therapy, or those with or without x-ray evidence of bone metastasis. (The data are summarized in table 3.) Stable patients with bone metastasis uniformly experienced diminution of bone pain and an improvement in performance status while on therapy.

TABLE 3.—Response to induction therapy*

	CAF-levamisole	CAF-placebo
Total	44	43
CR	3 (7 ± 8)	1 (2 ± 4)
PR	4 (9 ± 8)	7 (19 ± 12)
CR and PR	7 (16 ± 11)	8 (19 ± 12)
Stable disease	24 (55 ± 15)	22 (51 ± 15)
Responses and stable disease	31 (70 ± 14)	30 (70 ± 14)
Progressive disease	13 (29)	13 (30)
Pattern 1 responses	0/29	1/25 (4)
Pattern 2 responses	7/15 (47)	7/18 (39)
Patients who had responded to prior hormonal therapy	3/21 (14)	3/19 (16)
Patients who had not responded to prior hormonal therapy	4/23 (17)	5/24 (21)

*Values = No. of patients (% ± 95% confidence limit).

There were 61 patients who continued on therapy after the initial evaluation of response; 52 completed chemotherapy to the specified limit, with or without levamisole, or experienced disease progression during this period. Five patients refused therapy, two were removed from study before completion due to intercurrent disease, and two could not be evaluated due to inadequate data. The duration of treatment with chemotherapy appears comparable in the two groups.

At the time of this analysis, 72 of 97 patients evaluated for survival have died, with 26 patients alive or censored at last follow-up. The median duration of follow-up after randomization is 19.5 months. Analysis of the two treatment groups shows no significant difference in overall survival (20.3 versus 17.7 months, $P = 0.798$; fig 1), duration of disease control (6.7 versus 10.2 months, $P = 0.46$; fig 2), or duration of remission (13.3 versus 13.0 months, $P = 0.70$; fig 3). Because the number of patients in this study is relatively small, there is only a 75% chance of detecting a 50% increase in survival in the CAF-levamisole group. Inspection of figures 1–3 does not suggest any such difference. While accession of a larger number of patients would have strengthened the statistical reliability of our conclusions, we felt that the likelihood of finding a clinically important difference was small and closed the study at the present size. Patients with stable disease are grouped with those who achieved a CR or a PR in the analysis, since they fared significantly better than patients with progressive disease (median survivals, 23.5 versus 12.4 months, $P = 0.003$) but showed little difference from complete and partial responders (median survivals, 23.5 versus 28.1 months, $P = 0.70$). The survival of responders plus stable patients who received CAF-levamisole or CAF-placebo was nearly identical: 25.7 and 25.2 months, respectively, $P = 0.85$.

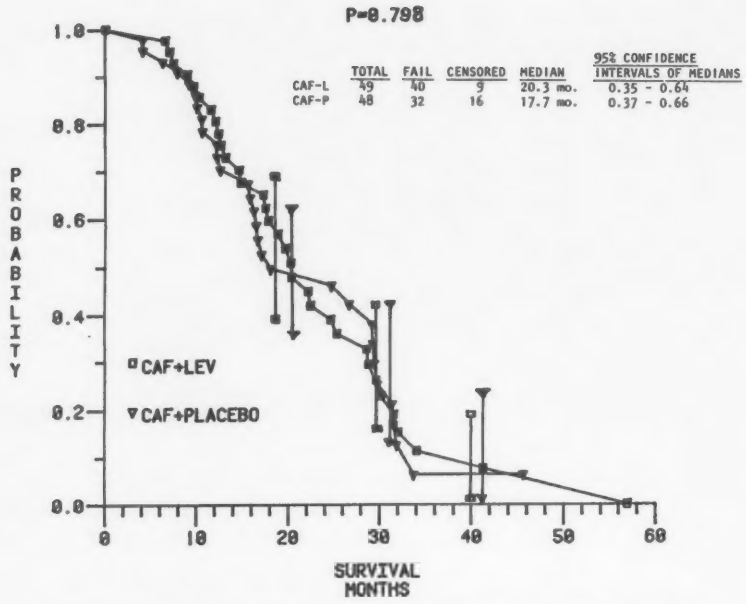

FIGURE 1.—Survival of all eligible patients. Vertical ranges shown are 95% confidence intervals of the curves at selected points.

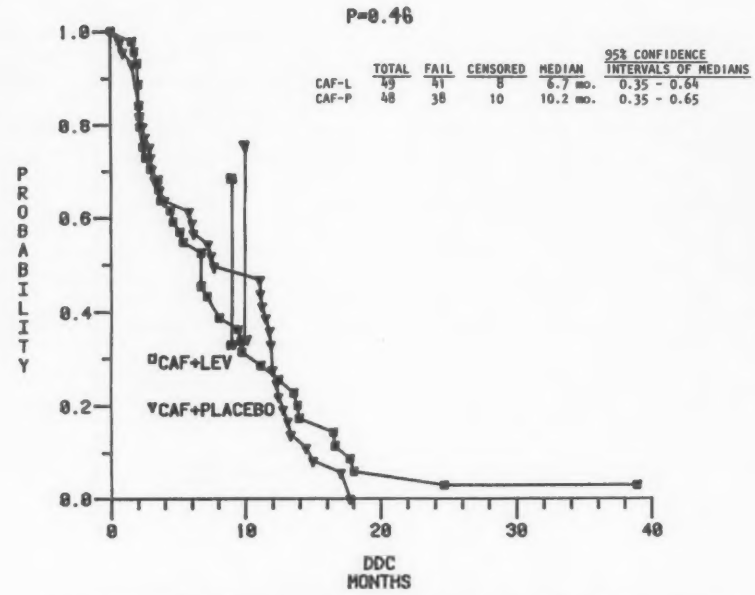

FIGURE 2.—Duration of disease control (DDC) in all eligible patients. Vertical ranges shown are 95% confidence intervals of the curves at selected points.

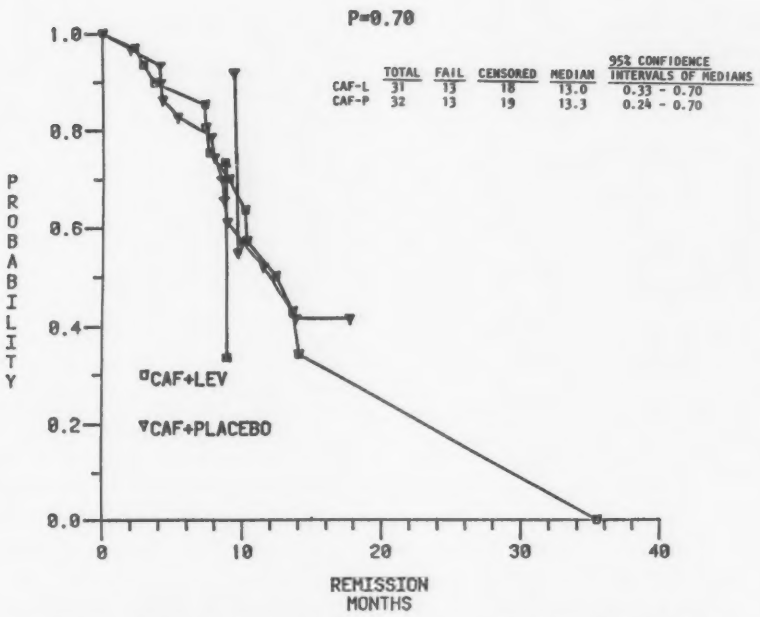

FIGURE 3.—Duration of remission in patients who had response or stable disease after induction treatment with CAF with or without levamisole. Vertical ranges shown are 95% confidence intervals of the curves at selected points.

The survival of patients with bone-only metastases (pattern 1) in this study is not significantly different from that of comparable patients treated with CAF in a previous SEG study (14): 20.3 versus 23.5 months, $P = 0.53$. Unlike the previous study, there was no difference in survival of those patients as compared to patients with pattern 2 disease (local-regional skin and soft tissue metastases): 20.3 versus 17.9 months, $P = 0.62$. The initial two doses of CAF were lower in the present study, but subsequent doses in both studies were modified according to patient tolerance using nearly identical dosage modification schemes. The overall survival of patients in this study appears to be somewhat longer than that of poor-risk patients with pulmonary and hepatic metastases who received CAF in another SEG study (15) (19.5 versus 14.0 months, $P = 0.0004$), lending some support to the contention that these patients are good-risk.

The toxic effects of the treatment were those which were expected and were usually tolerable. The primary ones were hematologic and gastrointestinal; details are listed in table 4. No difference in the amount of toxicity from either group was observed, except for the few patients who reported flu-like symptoms, allergy, fever, or joint pains after receiving levamisole. One patient experienced fever (104°F) and severe flu-like symptoms with each of the first two courses, which was attributed to levamisole. These symptoms did not reappear when CAF was subsequently given without levamisole. No such symptoms were reported in the CAF-placebo group. One patient in the CAF-levamisole group and two in the CAF-placebo group developed infections

TABLE 4.—Toxic effects*

Toxic effect	CAF-levamisole ($n = 46$)			CAF-placebo ($n = 46$)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Hemoglobin	18	6	1	7	3	10
Granulocyte count	5	11	16	8	12	10
Platelet count	5	1	3	4	2	—
Gastrointestinal	10	22	11	14	24	2
Cardiac	—	1	—	—	1	1

*Values = No. of patients.

associated with granulocytopenia; all recovered with treatment. Two patients developed congestive heart failure (one fatal) and one experienced arrhythmias which were attributed to doxorubicin. One ineligible patient later died of heart failure thought by the investigator to be due to mitomycin treatment.

The observed response rates for patients with pattern 1 and pattern 2 metastatic disease were lower than those seen in comparable patients in our previous study (14) (pattern 2 responses, 14 of 33 versus 26 of 32; pattern 1 responses, one of 54 versus eight of 50; and responses and stable disease, 37 of 54 versus 48 of 50). Granulocyte toxic effects observed in the two studies were comparable: mild-moderate, 37% versus 28%; severe, 22% versus 21%. The observed toxic effects suggest that intensity of therapy was comparable in the two studies. However, the dose rates in the two studies were different, since patients in the previous study began at full doses of therapy while those in this study began at half dose.

DISCUSSION

After the initial report (1), trials of levamisole were undertaken both in advanced breast cancer and in early disease as an adjuvant after mastectomy, with or without chemotherapy. Three studies of levamisole as an adjuvant to surgery indicated that it was not beneficial (16–18); in one of these, the patients who received levamisole actually fared worse than the control patients (17). In three of five published studies in advanced disease (19–23), however, patients who received levamisole in addition to cytotoxic chemotherapy survived longer than those who did not; in two they also had a higher rate of response to therapy. The most recent of these studies found shorter survival in patients who received levamisole (23).

The results obtained in this trial indicate that levamisole does not increase response rate or prolong remission duration or survival when given to patients with metastatic breast cancer in addition to chemotherapy with CAF. Some additional toxicity was observed, but no patient experienced agranulocytosis, as has been previously reported with levamisole (24). Prognostic variables which might confound the outcome did not appear to differ in the two groups of patients.

Examination of the reported duration of response and survival of patients treated in other studies provides some basis for comparison of the results. Table 5 lists results from published studies; in the trials reported by Hortobagyi et al (19), Klefström (20), and Stephens et al (22), patients who received levamisole survived longer than controls. However, their survival was shorter than that of controls in a Southwest Oncology Group (SWOG) study (23). The only stage IV study which suggests that survival of any group of patients exceeds 24 months is that of Klefström (20); examination of the survival data from that paper reveals that the median follow-up of those patients was only about 30 weeks. The estimate of survival in that paper, then, is at best tentative. The duration of survival in both positive and negative studies is about the same in treated patients and controls. Overall, no great difference in survival of any group is apparent; the data provide no convincing evidence that levamisole has a clinically significant effect in patients with metastatic (stage IV) breast cancer. The report of a beneficial role in stage III disease remains open to some question; that study (1) remains unconfirmed. Adjuvant studies in early stage primary breast cancer showed no benefit, as noted above (16–18).

Comparison of survival data from patients in this study with those of the previous SEG study (14) confirms that patterns of metastasis do identify patients with relatively long survival. The survival of patients with bone-only metastasis (pattern 1) whose disease remained stable on therapy was the same as those with objective tumor shrinkage on therapy; thus, these patients do relatively well on treatment despite the absence of measurable improvement and probably constitute a distinct biologically variant group of patients with metastatic breast cancer.

In summary, despite some theoretical basis and a few

TABLE 5.—Results of levamisole trials

Study	Ref No.	Duration of remission (mos)		Survival (mos)	
		Levamisole	Control	Levamisole	Control
Stage III					
Rojas et al	1	25	9	> 30	~ 26
Stage IV					
SEG (this study)		13	13.3	20.3	17.7
Hortobagyi et al	19	13	9	24	16
Patterson et al (responders only)	21	15	15	21	> 21
Klefström	20	18	11	> 24	21
Stephens et al (patients weighing < 70 kg)	22	—	—	20	13
Samal et al (SWOG)	23	4.5	9	15	20

positive clinical trials, we find no support for further use of levamisole as an adjuvant to chemotherapy of breast cancer.

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Hyponatremia and Other Toxic Effects During a Phase I Trial of Recombinant Human Gamma Interferon and Vinblastine[1,2]

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Recombinant human gamma interferon (Biogen) and vinblastine were administered in a phase I study. Side effects included fever and chills, nausea and vomiting, acute symptomatic hyponatremia, reversible myelosuppression, hepatitis, transient hypotension, congestive heart failure, renal insufficiency, and nonselective proteinuria. In most patients, additional host factors contributed to these toxic effects. Side effects occurred despite dose reduction; therefore, protocol accrual was prematurely closed. No correlation between serum concentrations and toxicity was noted. Median serum vinblastine concentration was 1.04 ng/ml; median serum interferon concentration was 17.3 IU/ml. [Cancer Treat Rep 70:1081-1084, 1986]

Recombinant human gamma interferon (rHuIFN-γ) differs substantially from alpha and beta interferons or other anticancer drugs and yet retains antineoplastic activity (1,2). In vitro and in vivo studies suggest that interferons combined with chemotherapeutic drugs can lead to enhancement of antineoplastic activity (3-7). However, no clinical studies have yet explored the combination of rHuIFN-γ and chemotherapy.

In this phase I study, we examined concomitant 5-day continuous infusions of vinblastine and rHuIFN-γ. Vinblastine administered by a 5-day infusion may be more effective than bolus dosing (8). Preliminary phase I trials show that IFN-γ is rapidly cleared from the serum (9). Thus, a 5-day continuous iv infusion of rHuIFN-γ and vinblastine was used in order to maintain a maximal cytotoxic concentration of both agents throughout the trial.

MATERIALS AND METHODS

rHuIFN-γ (specific activity, 2.4×10^7 units/mg of protein) was provided for this study by Biogen Inc (Cambridge, MA). Vinblastine sulfate (Velban) was purchased from Eli Lilly Co (Indianapolis, IN).

Schedule of Administration

The first three patients were treated with vinblastine, 1 mg/m^2/day iv, simultaneously with rHuIFN-γ, 1 mg/m^2/day. Five-day infusion cycles were to be administered every 3 weeks. The vinblastine dose was chosen in light of severe myelosuppression seen with 5-day infusions of vinblastine at dosages > 1.5 mg/m^2/day (9). rHuIFN-γ dosing was based on prior experience demonstrating that 7-day continuous infusion of rHuIFN-γ at 1 mg/m^2/day was well tolerated but that dosages of 3 mg/m^2/day were associated with significant toxic effects (hematologic and hepatic) (10). Fourteen-day continuous infusion of rHuIFN-γ is also associated with similar toxic effects at an rHuIFN-γ dosage of 1-3 mg/m^2/day (11). Patients who showed disease progression or major toxic effects would be taken off study. The daily dose of vinblastine was mixed in 1 L of 5% dextrose and water and infused continuously using an external mechanical pump. One-fourth of the daily rHuIFN-γ dose was mixed in 250 ml of 5% dextrose and water and infused continuously each 6-hour period.

Toxicity Definitions

Hypotension (decrease in systolic blood pressure of ≥ 40 mm Hg from baseline blood pressure), hyponatremia (decrease in serum sodium concentration of ≥ 10 mEq/L from baseline value) and Cancer and Leukemia Group B (CALGB) grade 3 or 4 toxic effects were regarded as major toxic effects.

Patients

Seven patients were entered on study (table 1). No patient had received prior interferon or vinblastine

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[2] Supported in part by Biogen Inc, Cambridge, MA, and the Jazz and Blues Fund.

[3] Joint Section of Hematology/Oncology, University of Chicago Hospitals and Michael Reese Hospital and Medical Center, IL; and Biogen Research Corporation, Cambridge, MA.

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TABLE 1.—Toxic effects and pharmacokinetic data on patients treated with rHuIFN-γ/VLB*

Patient No.	Age/ sex	Cancer diagnosis	Prior chemotherapy	Cycle No.	Toxicity (nonhematologic)	CALGB grade	Day first noted	Day resolved	C_{pss} VLB (ng/ml)	rHuIFN-γ (IU/ml)
					Group I†					
1	66/M	RC	No	I	Hyponatremia	—	1	2	0.78	9.9
					Proteinuria	3	6	—		
					Azotemia	3	5	—		
					Hyponatremia	—	4	5		
2	65/F	Breast	Yes	I	Arrhythmia	2	4	4	1.21	49.9
3	48/M	RC	Yes	I	Azotemia	3	20	30	1.8	17.6
					Hypoxemia	4	5	11		
					Group II‡					
4	56/M	RC	No	I	Hepatitis	4	3	21	0.78	11.9
5	46/M	RC	No	I	Hypotension	—	3	3	0.54	15.8
					Hepatitis	2	5	28		
				II	None				ND	ND
6	61/M	Urethral	Yes	I	None				0.92	9.6
7	58/M	RC	No	I	Hyponatremia	—	2	7	0.40	6.5
					Hypotension	—	1	2		
					Hypoxemia	4	3	5		
				II	Hyponatremia	—	3	4	1.9	ND
					Hypotension	—	4	5		
					Congestive heart failure	3	4	5		

*VLB = vinblastine; RC = renal cell; C_{pss} = steady-state plasma level; and ND = not determined.
†Group I = VLB at a dose of 1.0 mg/m^2/day and rHuIFN-γ at a dose of 1.0 mg/m^2/day.
‡Group II = VLB at a dose of 0.5 mg/m^2/day and rHuIFN-γ at a dose of 0.5 mg/m^2/day.

therapy, nor any therapy over the 4 weeks prior to study entry. Patients with active infections or brain metastases were ineligible. Adequate hematologic reserve (wbc count $\geq$ 3000/mm^3, platelet count $\geq$ 75,000/mm^3), and hepatic (serum bilirubin $<$ 2.5 mg/dl, serum SGOT and SGPT $\leq$ 100 IU/ml) and renal (creatinine $<$ 2.0 mg/dl) functions were required. Serum was drawn and analyzed for electrolytes, BUN, creatinine, cbcs, and vinblastine and rHuIFN-γ concentrations prior to the infusion of drugs and every 24 hours thereafter during the infusion. After the infusion, patients were followed weekly for clinical evidence of toxicity, and serum electrolytes, BUN, creatinine, and cbcs were also measured.

Pharmacologic Studies

Vinblastine concentrations were determined by radioimmunoassay by a modification of the method of Sethi et al (12) (sensitivity of the modified assay is 0.1–0.2 ng/ml). Antivinblastine antiserum was provided by Dr. Mary Root of Lilly Laboratories (Indianapolis, IN). Tritiated vinblastine was purchased from Amersham Corp (Arlington Heights, IL).

An ELISA was used to quantitate serum rHuIFN-γ levels. The assay sensitivity was $<$ 1 unit/ml. The method used a purified mouse monoclonal antibody (Meloy Labs, Clone No. 45/6) to natural HuIFN-γ. Antibody was coated on 96-well, flat-bottom polystyrene microtiter plates (Immulon 2, Dynatech Lab) by incubating 100 μl overnight in 0.05 M carbonate-bicarbonate buffer, pH 9.6, at room temperature. Plates were washed three times with phosphate-buffered saline (PBS) and 0.5% polysorbate 20, then with 300 μl of PBS and 1% gelatin at pH 7.2 for 1 hour, and then again as above. Samples of appropriately diluted serum were added to 100-μl duplicate wells and run along with a standard curve (from 0 to 1000 IU/ml of rHuIFN-γ as the standard) with appropriate controls. The plates were then incubated for 1 hour at 37°C and washed as before. Polyclonal rabbit IgG to rHuIFN-γ at 10 μg/ml in PBS, 1% gelatin, and 0.1% polysorbate 20 were added to the wells, incubated for 1 hour at 37°C, and followed by two washes. TMB (3,3′,5,5′-tetramethyl benzidine), 0.1 M acetate-citric acid (pH 4.9), and H_2O_2 were then added (100 μl/well) and the reaction was stopped with 100 μl/well of 2 M H_2SO_4. Absorbance (read at 450 nm) versus units per milliliter was plotted on semi-log paper. Unknowns were determined from the standard curve.

Because of the relatively long half-life of vinblastine (24 hours) (13), the means of the 96-hour and 120-hour serum levels were used to determine the steady-state plasma level (C_{pss}); rHuIFN-γ has a short half-life and therefore the mean of the daily levels was used to calculate its C_{pss}.

RESULTS

Toxicity

Major toxic effects (table 1) were noted in Patients 1–3; Patients 4–7 were therefore treated at a 50% dose reduction of both drugs. Severe toxicity continued, and protocol accrual was prematurely closed. All patients experienced fevers and chills; nausea and vomiting were noted in four patients. Only one patient experienced no major toxicity. No patient died during the therapy.

Two patients [Patient 1 (twice), and Patient 7 (twice)] experienced four episodes of disorientation and severe hyponatremia. Nadir serum sodium concentration (mean, 124 mEq/L; range, 118–127) developed at a median of 2 days after therapy initiation. Urine sodium concentration of Patient 1 was < 20 mEq/L when hyponatremia was noted (twice); Patient 7 was concurrently receiving a diuretic (twice). Possible associated factors included concurrent administration of excess free water (all episodes), diuretic (Patient 7), or chlorpropamide (Patient 1). In both patients, hyponatremia was rapidly reversed with free-water restriction and discontinuance of vinblastine and/or rHuIFN-γ infusion.

CALGB grade 3 hematologic toxicity (wbc count of 800/mm^3) developed in Patient 2. Therapy was discontinued, and the wbc count rose to 1900/mm^3 within 2 days. This patient had had extensive prior chemotherapy.

Two patients experienced severe respiratory difficulties. Patient 3 (with extensive pulmonary metastases from renal carcinoma) required intubation for 6 days. The patient had minimal shortness of breath prior to study entry. After extubation and discontinuance of study drugs, his pulmonary status stabilized. Subsequently, he received continuous-infusion vinblastine without respiratory compromise until death 4 months later.

Cardiac abnormalities [Patients 2, 5, and 7 (twice over two cycles)] rapidly reversed within 1 day of discontinuance of therapy. Excessive fluid administration and congestive heart failure in Patient 5 and continued diuretic use in the face of hypotension in Patient 7 (twice) may have contributed to toxicity.

Proteinuria and azotemia (CALGB grade 3) developed during the course of therapy in Patient 1 with diabetes and a prior nephrectomy. Patient 3 developed CALGB grade 2 renal insufficiency (3 weeks after completing therapy) after treatment with an aminoglycoside. Renal function returned to baseline 10 days later (after discontinuance of aminoglycoside therapy). CALGB grade 4 hepatitis was noted on Day 5 of therapy in Patient 4. This resolved within 3 weeks. All patients had progressive disease while on therapy.

Pharmacokinetics

The median C_{pss} of vinblastine in the seven patients was 1.04 ± 0.52 ng/ml; median serum rIFN-γ concentration was 17.3 ± 12.7 IU (table 1).

DISCUSSION

To our knowledge, this is the first report of the pharmacokinetics and toxic effects of concomitant 5-day infusions of rHuIFN-γ (Biogen) and vinblastine. Figlin et al (5) used alpha interferon and weekly bolus vinblastine in 24 patients with renal cell carcinoma; they reported greater toxicity than that observed with alpha interferon alone. Continuous 5-day infusion of vinblastine is usually associated with dose-related myelosuppression and peripheral neuropathy (8). Continuous infusion of rHuIFN-γ is associated with constitutional symptoms, fatigue, headache, transient elevation of serum hepatic transaminase levels, leukocytosis, and, rarely, cardiac ectopy. Transient confusion has also been noted during infusions of rHuIFN-γ, but simultaneous electrolyte changes were not mentioned (14). Two of our patients experienced symptomatic hyponatremia which appeared to be unique to the combination of the two drugs. Hyponatremia [felt to be due to syndrome of inappropriate antidiuretic hormone (SIADH)] has only rarely been observed during vinblastine (15) or rHuIFN-γ (16) infusion. In our patients the low urinary sodium concentrations suggest water intoxication, not SIADH, as the cause for the hyponatremia; it was minimized in later patients through strict free-water restriction during the course of therapy.

A second, unexpected toxic effect was respiratory distress in Patients 3 and 7. Respiratory difficulties have rarely been noted with single-agent vinblastine (17) or gamma interferon (16) therapy. Young et al (8) noted respiratory compromise (of probable allergic origin) in a patient receiving continuous vinblastine infusion, but in general, vinca alkaloid-induced bronchospasm is uncommon. After extubation, Patient 3 received 4 months of continuous-infusion vinblastine (18) without any further respiratory distress. Vinblastine was unlikely to have been the cause of his pulmonary dysfunction. The pulmonary toxicity could have been a result of a synergistic interaction.

Two patients had renal insufficiency; one of these had associated proteinuria. Interstitial nephritis has been described with alpha interferon treatment alone (19). Our patient had no evidence of acute interstitial nephritis in the urinary sediment although his proteinuria persisted despite discontinuance of therapy.

Our pharmacokinetic analysis showed that serum concentrations of vinblastine and rHuIFN-γ were no higher than those noted in prior studies of either drug alone (8,9), Thus, the unexpectedly severe toxic effects in this study can not be attributed to a pharmacokinetic interaction leading to elevated plasma levels of either drug. One hypothesis, that an interferon-vinblastine complex forms in vivo and induces toxicity, could be tested using in vivo model systems.

The combination of rHuIFN-γ and vinblastine is toxic at the dose and schedule employed. Lower doses or sequential scheduling may be necessary in the future in order to avoid major unexpected toxic effects. Prospective pharmacokinetic monitoring and/or a randomized phase I study design (ie, single-agent versus combination chemotherapy) may be necessary in order to discover the cause of such toxic effects.

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Randomized Comparisons of Radiotherapy and Carmustine Versus Procarbazine Versus Dacarbazine for the Treatment of Malignant Gliomas Following Surgery: A Southwest Oncology Group Study[1,2]

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Between 1977 and 1981, the Southwest Oncology Group entered 278 patients on a randomized study (SWOG 7703) to compare the effect of three different chemotherapeutic agents given in combination with radiotherapy (6000 rads over 7 weeks) following surgery for malignant gliomas. The chemotherapy regimens were: carmustine (BCNU)—80 mg/m² iv daily × 3 every 6 weeks; procarbazine (PCB)—100 mg/m² orally; or dacarbazine (DTIC)—175 mg/m² iv daily × 5 every 4 weeks. Patients were stratified according to age, and degree of resection, with no differences identified between groups. The response rates (complete plus partial) for BCNU and DTIC were significantly better than for PCB [BCNU, 39%; PCB, 13%; and DTIC, 38% ($P < 0.01$)]. The response duration and survival were somewhat better in patients treated with BCNU and DTIC, but compared to patients treated with PCB, the difference was not statistically significant. Median survival times were: BCNU, 45 weeks; PCB, 31 weeks; and DTIC, 49 weeks ($P > 0.3$). There were six toxic deaths with BCNU and four with PCB, most of which were due to infection associated with leukopenia. The high toxicity and minimal benefit of chemotherapy added to radiotherapy compared to historical results with radiotherapy alone suggest that combined treatment may not be indicated for some patients. [Cancer Treat Rep 70:1085-1090, 1986]

Patients with malignant primary CNS gliomas have a very poor prognosis (1-3). Treatment with surgery and radiotherapy prolongs patient survival and improves symptoms, but rarely results in long-term survival (4-6). Several trials of chemotherapy combined with surgery and radiotherapy have shown some benefit from the added drugs (6-9). The most widely employed agents used for the treatment of gliomas are the nitrosoureas, as they have shown activity in the control of recurrent gliomas (10). Both procarbazine (PCB) and dacarbazine (DTIC) have shown activity against tumors recurring following radiotherapy (11,12). To test whether PCB or DTIC might be superior to carmustine (BCNU), patients were randomized to treatment with radiotherapy plus one of these drugs in a three-arm prospective trial. This report represents the results of that clinical trial.

METHODS

Patient Accrual

Thirty-nine institutions participated in the study; 278 patients were entered between March 1977 and August 1981. Eligibility requirements included: histological confirmation of grade III or IV astrocytoma; radiotherapy and chemotherapy to be started within 4 weeks from the time of surgery; and no prior chemotherapy or radiotherapy. All patients were informed of the investigational nature of the study and gave written consent in accordance with institutional policy. All patients were adults.

Pretreatment parameters recorded for analysis included the following: age, sex, diagnosis (astrocytoma of grade III or IV), extent of surgery (biopsy, partial or

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complete resection), performance status, and neurological examination studies. At the time of entry into the study, patients were stratified according to age and extent of surgery and were then assigned to one of three treatment arms by the Southwest Oncology Group statistical office.

Pathological material and the operative note were submitted for review. Pathological review assigned patients to glioblastoma or anaplastic astrocytoma. Patients with other tumor types were excluded from review except for four patients with mixed tumors with predominance of glioblastoma histology. Anaplastic astrocytoma indicated tumors with increased cellularity, pleomorphism, and some endothelial proliferation, but no focus of necrosis. The diagnosis of glioblastoma was used for astrocytic tumors with necrosis whether or not there was pseudopalisading or endothelial proliferation.

Treatment

Radiation therapy was given using megavoltage apparatus with a minimum peak energy of 1 meV or ^{60}Co and a target (source)-skin or axis distance of 80 cm. Whole-brain irradiation was delivered using opposed lateral fields with care to include the entire contents of the middle cranial fossa with appropriate shielding of the orbits. Both fields were treated with delivery of 5 fractions per week. The tumor dose was calculated for the central axis of the treatment field at the mid-plane of the skull and was to be 6000 rads over a period of 7 weeks. The equipment of each institution was monitored by the Radiological Physics Center, Houston, TX. Port films on each patient were reviewed at the Quality Assurance Center at the University of Utah.

Chemotherapy was initiated 2 days prior to radiation therapy. All patients were given 10 mg/m^2/day of dexamethasone in divided doses during the course of radiation. Patients received the following: BCNU—80 mg/m^2/day $\times$ 3 every 6 weeks; PCB—50 mg on Day 1, 100 mg on Day 2, and then 100 mg/m^2/day in divided doses thereafter; DTIC—175 mg/m^2/day $\times$ 5 every 4 weeks. Chemotherapy was continued following the attainment of complete remission, partial remission, or stable disease for a total of 2 years or until relapse. The chemotherapy courses with BCNU and DTIC were repeated at 6 or 4 weeks, respectively, if the nadir wbc count and platelet count had been reached and evidence for recovery was present. Subsequent courses were modified according to the prior nadir blood cell counts. The dose of PCB was modified every 4 weeks according to wbc and platelet counts to achieve the maximum tolerable dose for each patient.

Response.—The parameters monitored in determining the patients' response to therapy included: tumor size [by computerized tomographic (CT) scan], neurologic function, and performance status. The duration of complete and partial responses was measured. Responses were defined as follows: *complete remission*—complete disappearance of measurable CNS tumors, normal neurologic function (or only abnormalities due to surgery), and absence of symptoms related to the tumor; *partial remission*—decrease in size of measurable CNS tumors on CT scan by 50%, combined with improvement in neurologic function by at least one level and improvement in tumor-related symptoms; *stable disease*—steady state of measurable disease without progression of symptoms; and *increasing disease*—increase in the size of the CNS tumor on CT scan by 50%, and deterioration of neurologic function by one level or worsening of tumor-related symptoms.

Since survival time was the most important parameter in this study, investigators were required to follow each patient until death, and to report the death on a supplementary off-study form.

Statistical methods.—Survival curves were estimated by the method of Kaplan and Meier (13), comparisons among the three curves were made by Breslow's test (14), and comparisons among two treatment groups were made by Gehan's test (15). Response rates were compared using chi-square tests.

RESULTS

A total of 278 patients were entered on the study. Thirty-five patients were not included in the final analysis for the following reasons: pathology review demonstrated incorrect tumor type (17 patients); radiotherapy major protocol violation (six); chemotherapy major protocol violation (three); and both radiotherapy and chemotherapy violations (nine). The remaining 243 patients were considered fully or partially evaluable and constitute the Valid Study Group used in analyses of response and survival data.

A comparison of the characteristics of the patients on each of the treatment regimens at the time of entry into study is shown in table 1. Stratification of patients by age (< 50 vs ≥ 50 years of age) and extent of surgery (biopsy vs partial; complete resection) assured that patients would be comparable with respect to these characteristics on each treatment. Pathology review of material submitted also demonstrated comparable numbers of patients with anaplastic astrocytomas and glioblastomas in each group. As the data in table 1 indicate, patients are comparable on each treatment regimen with respect to age, sex, histopathology status, and extent of surgery. There were no statistically significant differences between groups for any of the characteristics ($P > 0.20$ for all comparisons).

The response rates by treatment regimen are shown in table 2. The complete plus partial remission rates were 39% for patients receiving BCNU, 13% for patients receiving PCB, and 38% for patients receiving DTIC. The differences between these response rates were highly statistically significant ($P < 0.01$), in that patients treated with BCNU or DTIC had superior response rates compared to patients receiving PCB.

The duration of remission (complete plus partial) curves by treatment regimen for all evaluable patients

TABLE 1.—Comparison of patient characteristics according to treatment regimen*

Characteristic	Treatment regimen			
	BCNU	PCB	DTIC	Total
Evaluable patients	82	83	78	243
Median age (yrs)	55	55	54	55
Sex				
Male	57 (70)	55 (66)	57 (73)	169
Female	25 (30)	28 (34)	21 (27)	74
Histopathology				
Glioblastoma	57 (83)	60 (85)	53 (80)	170
Anaplastic astrocytoma	10 (14)	10 (14)	12 (18)	32
Mixed	2 (3)	1 (1)	1 (2)	4
Extent of surgery				
Biopsy	12 (15)	17 (20)	13 (17)	42
Partial or complete resection	70 (85)	66 (80)	65 (83)	201
Performance status†				
0	13	14	10	37
1	25	23	23	71
2	26	20	25	71
3	16	24	20	60
4	2	2	0	4

*Unless otherwise specified, values = No. of patients (% of patients with known values).

†Southwest Oncology Group criteria.

are shown in figure 1. There are no differences in duration of remission according to treatment regimen ($P > 0.3$ for all comparisons). There is a small group of the patients (20%) given BCNU who have longer remissions shown by the tail on the BCNU curve. The median durations of remission are given in table 2.

The survival curves by treatment regimen for all evaluable patients are shown in figure 2. There is no difference in survival between treatment groups ($P > 0.3$ for all comparisons); the median survival times are given by treatment regimen in table 2. Survival comparisons were also made for all eligible patients, including those with major protocol violations, and these showed no significant difference. There is no real basis for preferring one or the other of the treatment regimens according to survival experience from the time of start of treatment, but about 10% of patients treated with either BCNU or DTIC seem to have longer survival, giving a tail to the survival curves. Over 50% of the patients surviving > 104 weeks had anaplastic astrocytomas compared to 15% of the group as a whole.

The toxic effects reported by treatment regimen, both with respect to overall severity and according to the types of life-threatening and fatal toxicity reported for each treatment, are shown in table 3. The reports for toxicity were based upon the 260 patients who were eligible by pathological review and received any therapy. There were ten fatal toxic effects reported, six for BCNU and four for PCB. Of the six deaths in the BCNU arm, four were due to infection with granulocytopenia, one was due to hemorrhage with thrombocytopenia, and one was due to pulmonary toxicity. Two of the four fatalities with PCB were due to infection with granulocytopenia. Patients receiving DTIC had substantially less life-threatening and no fatal toxicity, but had substantially greater gastrointestinal toxicity with nausea and vomiting.

DISCUSSION

Several prospective randomized controlled studies have substantiated the value of postoperative radiation therapy when compared to surgery alone or surgery with chemotherapy, as summarized by Kelly et al (16). The addition of radiotherapy following surgery compared to surgery alone prolonged median survival from 4.0 to 8.7 months in the Brain Tumor Study Group Trial reported by Walker et al (6). Multiple studies testing the value of adjuvant chemotherapy in this setting have shown minimal further prolongation of median survival to 10–12 months, with the majority of benefit limited to patients in the 45–65-year-old age group (7,9,17,18). At the time the present study was undertaken, surgery followed by radiotherapy plus chemotherapy with BCNU was considered the "standard treatment" against which the addition of other chemotherapeutic agents would be compared.

Assuming that the major end-point for the evaluation of treatment regimens for malignant glioma patients is survival time, there is no significant statistical evidence favoring any of the treatments in the present study. Patients receiving PCB had significantly lower response rates than patients receiving BCNU or DTIC; however, the substantial difference in response rate translated into only a slight improvement in survival for BCNU- or DTIC-treated patients. Consequently, this randomized study was essentially negative with respect to detection of differences in survival experience among treatment regimens.

TABLE 2.—Responses, relapses, and survival by treatment regimen in the Valid Study Group*

End-points	Treatment regimen		
	BCNU	PCB	DTIC
Evaluable patients	82	83	76†
Responses			
Complete	23 (28)	7 (8)	15 (20)
Partial	9 (11)	4 (5)	14 (18)
Median duration of complete + partial (wks)	41	33	33
Total relapses‡	25 (78)	11 (100)	23 (79)
Survival			
Deaths	70	77	62
Percentiles of time (wks)			
75	15	16	14
50	45	31	49
25	76	61	82

*Unless otherwise specified, values = No. of patients (%).

†For 2 patients, follow-up time was not adequate to calculate response rate and survival.

‡Among complete + partial responders.

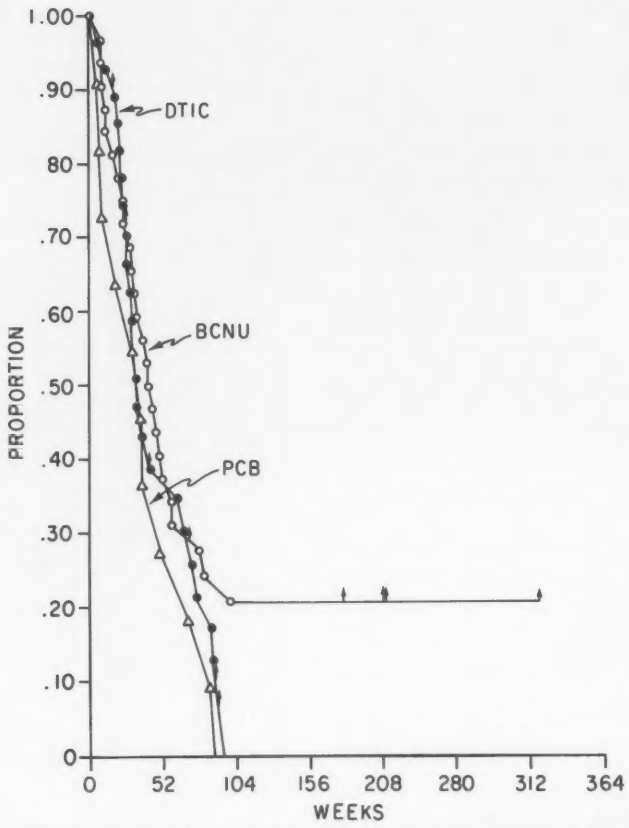

FIGURE 1.—Duration of remission (complete + partial) for the 3 treatment groups. Treatment 1 (BCNU)—32 patients; Treatment 2 (PCB)—11 patients; Treatment 3 (DTIC)—29 patients.

With the given number of patients on each treatment regimen in the Valid Study Group, there was a reasonably high probability (> 80%) of detecting differences in the percent of patients surviving of 20%-22% at a particular time after the start of treatment (statistical significance level, 5%). Consequently, we can be reasonably certain that there is no survival difference of ≥ 20% between treatment regimens.

The results of treatment in this clinical trial judged by patient survival compare favorably to several randomized studies using a control treatment arm of surgery plus radiotherapy only and to trials using surgery, radiotherapy, and BCNU chemotherapy (6,7,9,17). The significant toxicity experienced by patients treated with any of the three chemotherapeutic agents must be balanced against the minimal added benefit to survival and quality of life of these patients. In this study, that added benefit was obtained at a high cost in toxic side effects. A similar level of toxicity was reported in the Radiation

TABLE 3.—Toxic effects reported by treatment regimen*

Characteristic	Treatment regimen		
	BCNU	PCB	DTIC
Eligible patients	87	91	82
Overall severity			
Fatal	6 (7)	4 (4)	0 (0)
Life-threatening	5 (6)	6 (7)	1 (1)
Severe	21 (24)	26 (29)	21 (23)
Types of life-threatening and fatal toxic effects			
Granulocytopenia	4	5	
Thrombocytopenia	7		1
Pulmonary	1	1	
Nausea/vomiting		1	
Anemia		1	
Gastrointestinal		1	
Other	1	1	

*Values = No. of patients (%).

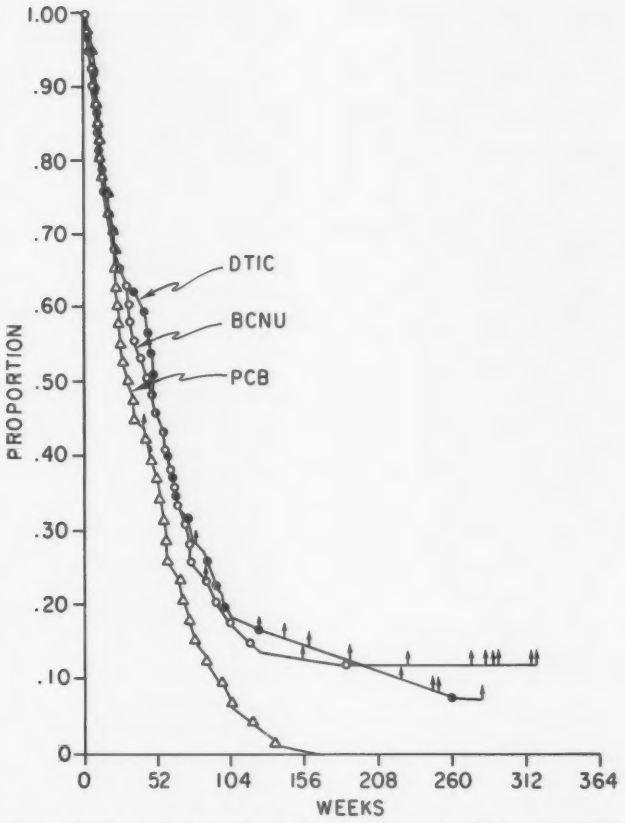

FIGURE 2.—Median survival of patients in the 3 treatment groups. Treatment 1 (BCNU)—45 wks; Treatment 2 (PCB)—31 wks; Treatment 3 (DTIC)—49 wks. $P > 0.3$.

Therapy Oncology Group-Eastern Cooperative Oncology Group study (9). Clearly, better drugs or less toxic ways of using them are needed before any major advance can be accomplished in the treatment of patients with malignant gliomas.

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Trial of the Combination of Mitomycin, Vindesine, and Cisplatin in Patients With Advanced Non-Small Cell Lung Cancer[1,2,3]

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In prior trials, mitomycin, vindesine, and cisplatin have each been shown to have reproducible antitumor activity as single agents when used in the treatment of patients with non-small cell lung cancer. The two-drug combinations of vindesine plus high-dose cisplatin or mitomycin have shown an improved major response rate and manageable toxicity in prior trials. In this report, 90 patients with stage III non-small cell lung cancer were treated with the three-drug combination of mitomycin (8 mg/m^2), vindesine (3 mg/m^2), and high-dose cisplatin (120 mg/m^2). Eighty-seven patients (97%) were adequate for both response and toxicity. Major objective responses occurred in 60% of the patients. The toxicity of this regimen was predictable and manageable when established supportive care measures were employed. Based on the response rate observed, the combination of these three agents merits further study in randomized trials against other chemotherapeutic regimens and consideration of its use in adjuvant and preoperative settings. [Cancer Treat Rep 70:1091-1096, 1986]

Since 1970, the English language medical literature has contained formal reports of at least 134 single-agent phase II trials in patients with advanced non-small cell lung cancer (1). Only five of the 51 drugs evaluated demonstrated a major objective response rate of $\geq$ 15% when tested in at least 14 patients: cisplatin, ifosfamide, mitomycin, vinblastine, and vindesine (1). With the small number of potentially useful drugs available, one approach to the treatment of advanced non-small cell lung cancer is to use only those agents with reproducible single-agent activity of at least 15% and to select agents for use in combinations that can be safely given at the established schedules and doses for each drug as defined in the prior phase II trials. Moreover, treatment programs must strictly follow proven methods to ameliorate or lessen drug-induced toxicity. The use of combinations of active drugs at established doses and schedules with proven supportive care measures appears to provide the optimal method to investigate whether chemotherapy can improve the control of advanced non-small cell lung cancer.

Vindesine has been evaluated in 449 patients previously untreated with chemotherapy, and an overall major response rate of 18% has been reported (2-14). In two randomized trials, vindesine as a single agent demonstrated superior anticancer activity in lung cancer patients when compared to combinations of conventional agents that individually do not have reproducible single-agent activity: cyclophosphamide, lomustine, and methotrexate (14) and doxorubicin and cyclophosphamide (15). Cisplatin has demonstrated an overall major response rate of 24% when tested in 126 non-small cell lung cancer patients previously untreated with chemotherapy (16-21). Mitomycin has demonstrated major antitumor activity in 18% of 115 patients with non-small cell lung cancer who had not received prior chemotherapy (22-25). Due to the differing patterns of toxicity for vindesine and cisplatin, both can be combined at their established doses. The combination of vindesine and high-dose cisplatin has yielded an overall response rate of 32% in seven prior randomized trials studying 377 patients (12,26-31). The combination of mitomycin plus vindesine has also been studied and has produced a major response rate of 29% in 173 patients in four trials (31-34).

Although vindesine, cisplatin, and mitomycin each have potentially serious toxic effects, experience with their use as single agents and in two-drug combinations

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has led to the development of doses, schedules, and attenuation schedules for the drugs that safely allow their use. Moreover, these same trials and related research efforts have uncovered effective methods to manage or prevent cisplatin-induced vomiting and renal toxicity. The use of established drug schedules and supportive care measures is imperative to ensure both the safe conduct of combination chemotherapy studies and maximum patient comfort.

In view of the demonstrated single-agent activity of mitomycin, vindesine, and cisplatin and the apparently additive antitumor effect of vindesine plus cisplatin or mitomycin when used in combination (and the acceptable toxicity of the drugs when used in two-drug combinations employing their established phase II doses and schedules), a trial of the three-agent combination of mitomycin, vindesine, and cisplatin was undertaken in patients with stage III non-small cell lung cancer. The objectives of this trial were to determine the major objective response rate for the regimen and to define the side effects of this treatment program.

PATIENTS AND METHODS

From August 1983 to August 1984, 90 consecutive patients with histologically confirmed non-small cell lung cancer meeting the eligibility characteristics below were entered. There were no concurrent radiotherapy protocols or combination chemotherapy trials studying similar patients during the time of this investigation. All patients had stage III disease as established by the criteria of the American Joint Committee for Cancer Staging and End Results Reporting (35). Patients were required to have either bidimensionally measurable indicator lesions or evaluable (29,36) lesions visible on roentgenographic studies or physical examination. Indicator lesions could not be included in areas of prior irradiation. All patients were required to have a Karnofsky performance status > 50%; creatinine clearance > 65 ml/minute; leukocyte count > 4000/mm^3; platelet count > 150,000/mm^3; bilirubin < 2.0 mg/dl; no clinical congestive heart failure; and clinically normal auditory function. Only patients not previously treated with chemotherapy were eligible. Informed consent was obtained.

The characteristics of the 87 adequately treated patients (97% of the patients entered) are shown in table 1. Pretreatment patient characteristics of potential prognostic significance include: 59% of patients had an initial Karnofsky performance status > 70%; 28% of patients were women; 21% of patients had bone metastases; 31% of patients had two or more organs involved with metastatic disease; and 59% had an elevated serum LDH. Thirty-two percent of entered patients were stage III M0. In the last previously reported trial of cisplatin-based chemotherapy at this institution (29), 14% of patients had stage III M0 disease. In the current trial, 26% of entered patients had limited disease, ie, "disease encompassable within a single tolerable radiation port."

TABLE 1.—Characteristics of 87 patients

Characteristic	No. of patients (%)
Median age (yrs): 55	
Male/female	63 (72)/24 (28)
Karnofsky performance status	
60%–70%	36 (41)
80%–100%	51 (59)
Histologic subtype	
Adenocarcinoma	54 (62)
Epidermoid carcinoma	22 (25)
Large cell carcinoma	11 (13)
Weight loss (as a % of patient's usual weight)	
< 6%	56 (64)
≥ 6%	31 (36)
Prior treatment	
Radiotherapy	5 (6)
Surgery	4 (5)
Radiotherapy and surgery	3 (3)
Stage III M1	59 (68)
Limited disease	23 (26)
No. of extrathoracic metastatic sites	
0	28 (32)
1	31 (36)
2	20 (23)
≥ 3	8 (9)
Sites of distant metastases	
Lung	19 (22)
Bone	18 (21)
Extrathoracic lymph nodes	18 (21)
Pleura	12 (14)
Liver	8 (9)
Subcutaneous	7 (8)
Brain	6 (7)
Adrenal	5 (6)
Other	4 (5)
Serum LDH > normal	50 (57)

Before treatment, all patients had a complete medical history, physical examination, cbc, 12-channel biochemical profile, serum creatinine, 24-hour urine collection for creatinine, and chest roentgenogram. Radionuclide and/or computed tomographic scans were done only when clinically indicated by history, physical examination, or routine biochemical testing. Patients had weekly histories, physical examinations, and cbcs for the first 5 weeks. Thereafter, these evaluations were repeated every 2 weeks. Biochemical tests, creatinine clearance determinations, and chest roentgenograms were repeated before each cisplatin dose.

Cisplatin was given with strict adherence to the well-established method of Hayes employed in prior trials of high-dose cisplatin in non-small cell lung cancer (18,26,29). Patients received cisplatin at a dose of 120 mg/m^2 of body surface area or 3 mg/kg, whichever was less. Cisplatin doses were repeated on Day 29 and then every 6–8 weeks. Hydration with 2–3 L of 5% dextrose in 0.45% NaCl was initiated 12–18 hours prior to therapy. Immediately before cisplatin, 12.5 g of mannitol was

given as a rapid iv injection. Cisplatin was then administered over 20 minutes. Over the ensuing 6 hours, all patients received an infusion of 20% mannitol at a rate of 50 ml/hour and 5% dextrose in 0.45% NaCl. All patients initially received iv metoclopramide (3 mg/kg) ½ hour before and 1½ hours after cisplatin and dexamethasone (20 mg iv), with either diphenhydramine (50 mg iv) or lorazepam (1.0–1.5 mg/m^2) ½ hour prior to cisplatin (37,38).

Patients were given vindesine (3 mg/m^2) (supplied by Eli Lilly and Company, Indianapolis, IN) weekly for 5 weeks (Days 1, 8, 15, 22, and 29) and then every other week. Mitomycin (8 mg/m^2) was administered at the time of the first three cisplatin doses (Days 1, 29, and 71), for a total of three doses. Only three doses of mitomycin were given, each with dexamethasone, in an effort to lessen or prevent mitomycin-induced lung toxicity. Chemotherapy with cisplatin was attenuated by 50% if the subsequent creatinine clearance was between 45 and 54 ml/minute. Cisplatin was withheld if the creatinine clearance fell to < 45 ml/minute, if the leukocyte count fell to < 2000/mm^3, or if there was evidence of marked neurotoxicity or ototoxicity. Therapy with vindesine was attenuated by 50% for a leukocyte count between 2000 and 2900/mm^3, for a platelet count < 140,000/mm^3, or if there was evidence of moderately symptomatic (2+) neurotoxicity. Vindesine was withheld if the leukocyte count was < 2000/mm^3, platelet count was < 100,000/mm^3, bilirubin was > 2.5 mg/dl, or if there was evidence of marked neurotoxicity. Mitomycin was withheld if the leukocyte count was < 3000/mm^3, platelet count was < 100,000/mm^3, or if the creatinine clearance fell to 45 ml/minute. If a dose of vindesine or cisplatin was withheld, the dose for that date was recorded as zero and the next dose was given on schedule following the above guidelines. If a dose of mitomycin was withheld, it was given at the time of the next scheduled vindesine dose if clinical and laboratory parameters permitted.

Therapeutic responses were determined as previously described (29). The major response categories were complete response, partial response (measurable indicator lesions), and disease improvement (evaluable indicator lesions). Standard criteria were used for patients with measurable indicator lesions (39). Response categories for patients with evaluable disease were complete remission, disease improvement, no change, and disease progression, as previously described (29), and required the agreement of three physicians, including the reference radiologist. Forty-one patients (47%) had measurable lesions and 46 patients (53%) had evaluable indicator lesions. Major response rates ($P = 0.83$), response durations ($P = 0.88$), and survival durations ($P = 0.96$) did not differ significantly between patients with evaluable and measurable indicator lesions in this trial. Patients were considered adequate for response assessment if they received at least one dose of cisplatin and mitomycin and three doses of vindesine.

All patients were prospectively evaluated from the time of initiation of chemotherapy until objective documentation of disease progression. Response duration and survival were calculated from the first day of treatment (39). Response ended on the date of the first objective measure of disease progression (39). The significance of observed differences was assessed by the chi-square test. Tests for differences in response and survival durations were done using the log-rank test (40).

RESULTS

Eighty-seven of the 90 patients (97%) who entered this trial are adequate for evaluation of response. Two patients received a less than adequate course of chemotherapy (defined above) and one was lost to follow-up. The median follow-up time is 10.5 months for all patients, with a maximum of 21 months. The median number of doses of chemotherapy administered to all patients for mitomycin, vindesine, and cisplatin was three, ten, and three doses, respectively. As shown in table 2, the overall major objective response rate was 60% (52 responses among 87 patients). Six patients (7%) had complete response (three of these six were pathologically confirmed by thoracotomy). The major response rate for adenocarcinoma was 50%, for epidermoid carcinoma was 77%, and for large cell carcinoma was 73% ($P = 0.06$). The median duration of response was 6.5 months for the 52 patients with complete and partial responses and disease improvement.

The median survival was 11 months for all 87 patients in the study. There was a significant difference in the median survival between those patients with stage III M1 disease (9.5 months) as compared to those with M0 disease whose median survival has not yet been reached and will exceed 13 months ($P = 0.008$). The median survival of those patients with < 6% pretreatment weight loss (15 months) was improved over those patients reporting > 6% weight loss (7.5 months) ($P = 0.003$). The median survival durations did not differ significantly comparing the following: patients with a Karnofsky performance status 60% and 70% (9.0 months) and performance status 80%, 90%, and 100% (13.5 months) ($P = 0.17$); and patients with adenocarcinoma (10.5 months), epidermoid carcinoma (16 months), and large cell carcinoma (9.0 months) ($P = 0.38$). The median survival for

TABLE 2.—Objective responses observed in 87 patients

Response	No. of patients (%)
Major response	52 (60)
Complete remission	6 (7)
Partial remission* or disease improvement†	46 (53)
No major response	35 (40)
No change	26
Disease progression	9

*Patients with measurable indicator lesions only.
†Patients with evaluable indicator lesions only.

TABLE 3.—Observed toxic effects in 87 patients

Toxic effect	No. of patients (%)
Leukocyte count nadir (cells/mm^3)	
> 3000	14 (16)
2100–2900	26 (30)
1000–2000	34 (39)
< 1000	13 (15)
Platelet count nadir (cells/mm^3)	
> 100,000	58 (67)
50,000–100,000	16 (18)
< 50,000	13 (15)
Highest serum creatinine (mg/dl)	
< 1.4	37 (43)
1.5–2.0	35 (40)
2.1–3.4	12 (14)
> 3.5	3 (3)
Maximum degree of peripheral neuropathy	
None	29 (33)
Mild	29 (33)
Moderate (interferes with function)	26 (30)
Severe	3 (3)

patients with complete or partial responses or disease improvement was 16 months and for the group of patients who had no change or disease progression was 6.5 months.

The toxic effects observed during this trial are shown in table 3. No patient died as a result of treatment. The median leukocyte count nadir was 1900/mm^3. Fifteen percent of all patients had a leukocyte count nadir < 1000/mm^3. Fourteen patients (16%) required readmission to the hospital for the treatment of fever occurring during a period of drug-induced leukopenia. Only 15% of patients had platelet counts < 50,000/mm^3 at any time in the study. No patient required a platelet transfusion.

The maximum serum creatinine of 43% of patients never exceeded the upper range of normal. The highest serum creatinine recorded was < 2 mg/dl in 83% of patients, with the highest serum creatinine for any patient being 4.9 mg/dl, and none had grade 3 or 4 renal toxicity as defined by World Health Organization criteria (39). No patient developed symptomatic renal dysfunction or required dialysis.

Thirty-four percent of patients developed a peripheral neuropathy that necessitated attenuation of chemotherapy. Three patients (3%) developed marked neuropathy requiring the cessation of chemotherapy; two of these patients had clinical evidence of diabetic sensory neuropathy prior to study entry. Some degree of alopecia was seen in all patients.

Sixty-eight patients (78%) were treated on formal antiemetic protocols and had their amount of emesis carefully quantitated by direct observation during the first 24 hours after cisplatin. Sixty-three percent of these patients had no vomiting, and 87% experienced two or fewer emetic episodes (37,38) during their initial cisplatin course. These patients also had careful measurements of the subjective effects of therapy during this initial 24-hour period. Mean "satisfaction" scores ranged from 71 to 91/100; > 92% of patients asked to receive the same antiemetic regimen again with subsequent courses of cisplatin (38).

Twenty-nine patients (33%) had mild and seven patients (8%) had moderate clinical evidence of hearing loss in the study. Three patients developed transient hyponatremia following cisplatin administration. Three patients developed cutaneous ulcers at sites of chemotherapy administration; all of these improved with conservative management. Three patients reported an episode of orthostatic dizziness within 1 week after receiving cisplatin. No specific etiology was apparent. Two patients developed hypersensitivity reactions following cisplatin. Both patients had received seven doses of the drug prior to the development of hypersensitivity symptoms. Mild constipation was seen in many patients and always responded well to laxatives. Two patients who had received three prior doses of mitomycin developed a self-limited episode of acute dyspnea shortly after receiving vindesine. This reaction has been previously characterized (41,42). We did not observe any instances of the hemolytic-uremic syndrome or mitomycin-induced chronic pulmonary dysfunction.

DISCUSSION

Vindesine and high-dose cisplatin both have demonstrated a ≥ 15% major response rate in single-agent phase II trials in non-small cell lung cancer. The response rates observed when these two drugs are used in combination suggest that their antitumor effectiveness is additive and that their toxicity patterns are dissimilar. In the two prior trials at our institution, these two agents in combination have produced response rates of 33% and 40%. The present trial tested the hypothesis that the rate of response of the combination of vindesine plus cisplatin could be increased by adding a third drug which also had demonstrated activity as a single agent. Mitomycin was chosen as a third agent because of its documented activity in prior single-agent trials, limited acute toxicity, and proven additive antitumor activity and safety when used in combination with vindesine. The 60% major objective response rate observed in this trial of the three-drug combination of mitomycin, vindesine, and cisplatin appears to support the contention that combinations of individually active drugs can produce additive antitumor effects in non-small cell lung cancer patients. The 95% confidence limits for the predicted true response rate for the regimen based on the observed data range from 50% to 70%. The observed response rate in this trial is similar to that of other investigators reporting on the drug combinations of mitomycin, high-dose cisplatin (≥ 75 mg/m^2), and the vinca alkaloid vinblastine (43–45). In these three trials, an overall major objective response rate of 65% was observed in 78 patients (43–45).

Prior trials of vindesine plus cisplatin at our institution yielded median durations of major response of 8.6

and 12.0 months and median survival times for all patients of 9 and 10 months (26,29). A median response duration of 6.5 months and median survival of all patients of 11 months were observed in this trial. Based on these observations, the principal advantage of the addition of mitomycin to the vindesine plus cisplatin combination appears to be that a major response can be achieved in most patients. However, final conclusions regarding comparison of the two- and three-drug regimens await the completion of a random assignment trial.

The observed toxicity in this study was comparable to that noted in prior trials employing the two-drug combination of vindesine plus high-dose cisplatin. Myelosuppression was moderately increased over the vindesine and cisplatin regimen (26,29) but similar to that observed with the combination of vinblastine plus cisplatin (29). Nephrotoxicity was not increased by the addition of mitomycin to the vindesine plus cisplatin regimen. During the trial, special care was taken to ensure that the protocol and drug attenuation schedules were strictly followed and that proven supportive care measures were employed, including: adequate hydration and mannitol-induced diuresis to prevent cisplatin-induced nephrotoxicity, the use of established doses and schedules of antiemetic medications to control cisplatin-induced vomiting, and the use of dexamethasone to possibly lessen or prevent mitomycin-induced pulmonary toxicity as reported in a preliminary trial (46). Despite the serious potential adverse effects of each of the three agents in the treatment regimen, there were no treatment-related deaths.

The major response rate with the three-agent combination of vindesine, cisplatin, and mitomycin in the dose and schedule employed in this trial is higher than that observed in previous trials of two-drug regimens in similar patients with stage III non-small cell lung cancer. The toxic effects observed with the addition of this third agent were predictable and manageable. Severe toxicity can be minimized or avoided using available methods of supportive care. These data warrant the initiation of randomized trials comparing the three-drug combination of mitomycin, vindesine, and cisplatin to the two-drug regimen of vindesine plus cisplatin and to other active regimens. If the formal comparison trials support this increased activity, it would appear that this regimen would merit further study in multimodality treatment programs.

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Phase II Trials of Cisplatin and Piperazinedione as Single Agents in the Treatment of Advanced or Recurrent Non-Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study[1,2]

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A total of 42 patients with advanced or recurrent carcinoma of the cervix, other than squamous cell carcinoma, were entered onto two phase II studies by the Gynecologic Oncology Group. Of 16 patients registered to receive piperazinedione at a dose of 9 mg/m² iv every 3 weeks, two were inevaluable for response because of the lack of measurable disease. Of the remaining 14, two (14%) had complete response. Adverse effects were limited to myelosuppression, nausea and vomiting, and nephrotoxicity. Among 26 patients registered to receive cisplatin, three were deemed ineligible and three were inevaluable for the study. Of the remaining 20 patients, one (5%) had complete response and three (15%) had partial response. Primary adverse effects included myelosuppression, frequent nausea and vomiting, and nephrotoxicity. The most common histologic subtypes noted were adenocarcinoma and adenosquamous carcinoma, and responses were noted among patients with each subtype on each drug. Both drugs appear to possess moderate activity against non-squamous carcinoma of the cervix. [Cancer Treat Rep 70:1097–1100, 1986]

Although cancer of the uterine cervix has been the subject of a number of clinical trials of the use of chemotherapy for advanced or recurrent disease (1), no study to date has attempted to separate the non-squamous carcinomas from the vast majority of squamous cell carcinomas to determine whether these lesions respond differently to systemic therapy. A previous review of the general subject of chemotherapy in cervix cancer briefly described preliminary results of two such trials by the Gynecologic Oncology Group (GOG) (2). This report describes the final analysis of a study of two agents in patients with advanced or recurrent non-squamous carcinoma of the cervix.

MATERIALS AND METHODS

A total of 42 patients with advanced or recurrent carcinoma of the cervix of histologic type other than squamous cell carcinoma were entered onto two phase II studies between January 1977 and November 1979 by member institutions of the GOG. Three patients were deemed ineligible for the study: one because of a primary site other than the cervix, one because of no documented primary, and one because of GOG performance status of 4 at time of entry. Two patients were deemed inevaluable: one because of insufficient data submitted to permit evaluation and a second because she never

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received treatment. Of the remaining 37 patients, three were inevaluable for response because of the lack of measurable disease. The remaining 34 patients each met the following criteria: (*a*) histologically documented advanced or recurrent carcinoma of the cervix, of histology other than squamous cell carcinoma, with confirmation by GOG Pathology Committee review; (*b*) objectively measurable disease; (*c*) adequate bone marrow reserve as judged by wbc count $\geq 4000/\mu l$ and platelet count $\geq 150,000/\mu l$; (*d*) adequate renal (normal BUN and serum creatinine) and hepatic (normal SGOT and bilirubin) function; (*e*) a GOG performance status of at least 3 (Karnofsky, 30% or better); and (*f*) recovery from the effects of prior therapy.

Patients receiving piperazinedione were given 9 mg/m^2 iv every 3 weeks until disease progressed or adverse effects prevented further therapy. Appropriate dose modifications were carried out according to the degree of severity of the dose-limiting effect of myelosuppression. If grade 3 or greater toxicity (wbc count $< 2000/\mu l$ and/or platelet count $< 50,000/\mu l$) was observed, the dose was reduced by 33%; toxicity of grade 1 or less (wbc count $\geq 3000/\mu l$ and platelet count $\geq 100,000/\mu l$) required a 33% dose increase. Prolonged myelosuppression (failure to recover to wbc count $\geq 3000/\mu l$ or platelet count $\geq 100,000/\mu l$ by 4 weeks after preceding drug dose) also mandated a dose reduction of 33%.

Patients receiving cisplatin were given 50 mg/m^2 iv at a rate of 1 mg/minute every 3 weeks. Each dose was preceded by 12 hours of iv hydration with normal saline at a rate of at least 100 ml/hour and followed by 24 more hours of hydration with the same fluids at the same rate. The drug was continued until disease progressed or adverse effects prevented further therapy. Appropriate dose reductions were carried out in these patients also for excessive adverse effects. Grade 3 myelosuppression required a 25% dose reduction, while grade 4 myelosuppression (wbc count $< 1000/\mu l$ and/or platelet count $< 25,000/\mu l$) mandated a 50% reduction in dose. Prolonged myelosuppression as defined above called for a 25% dose reduction. Renal impairment manifested by BUN ≥ 40 mg/dl and or serum creatinine ≥ 2 mg/dl required cessation of drug therapy. Ototoxicity or significant neurotoxicity also called for drug cessation.

Patients were seen at least every 3 weeks for evaluation of measurable disease and adverse effects and for further therapy, if feasible. A patient was considered to be evaluable for response if she received one drug dose and lived at least 3 weeks, whereas any patient receiving any drug was considered evaluable for adverse effects.

Standard GOG response criteria were used (3). Survival was defined as the time from initiation of drug therapy to death or date of last contact.

RESULTS

Piperazinedione Therapy

Patient characteristics.—Sixteen patients were entered onto study to receive piperazinedione (table 1). Two were inevaluable for response because of the lack of measurable disease. These two were evaluated for adverse effects only. Of the remaining 14, seven had adenosquamous carcinoma, six had adenocarcinoma, and one had an unclassified carcinoma. Eight patients had disease confined to the pelvis at the time of initiation of drug therapy, while six had evidence of extrapelvic metastases (three in lungs, one in lungs and liver, one in abdomen, and one in supraclavicular nodes). Only six of the 14 patients had undergone prior surgical treatment, but 13 of the 14 had received prior radiotherapy. Eight of the 14 had received prior chemotherapy, and two had received hormonal therapy directed at the neoplasm. At the time of study entry, 12 of the 14 patients had GOG performance status 2 or better.

TABLE 1.—Characteristics of the 16 patients registered to receive piperazinedione

Characteristic	No. of patients (%)
Total	16
Inevaluable for response	2
Performance status	
0–2 (Karnofsky, 50%–100%)	12
3 (Karnofsky, 30%–40%)	2
Disease site	
Pelvis only	8
Extrapelvic	6
Histology	
Adenosquamous carcinoma	7
Adenocarcinoma	6
Carcinoma not otherwise specified	1
Prior therapy	
Surgery	6
Radiotherapy	13
Hormonal therapy	2
Chemotherapy	8
Response	
Complete	2 (14)
Stable disease	2 (14)
Increasing disease	10 (72)
Adverse effects*	
Leukopenia	6
Thrombocytopenia	4
Nausea and vomiting	6
Azotemia	2†
Other	2

*16 evaluable patients.
†1 grade 4.

Response.—Of the 14 patients evaluable for response, two (14%) manifested complete response, two (14%) had stable disease, and 10 (72%) had increasing disease. Among the seven patients with adenosquamous carcinoma, one complete responder was observed, with the response lasting 3 months and the patient surviving 11 months. The patient's assessable disease was in the lung. Among six patients with adenocarcinoma, one complete responder was also observed. This patient's measurable disease was confined to the pelvis. The response lasted 3 months, and the patient died very shortly after documented progression. The single patient with unclassi-

fied carcinoma manifested stable disease. The overall median survival for the entire population was 2 months with a range from 0.5 to 12.5 months.

Adverse effects.—Six patients manifested leukopenia (five, grade 1; and one, grade 3), with the lowest recorded wbc count being 1400/μl. Four of the six manifested thrombocytopenia (three, grade 2; and one, grade 3). The lowest recorded platelet count was 42,500/μl. No sepsis or hemorrhage related to myelosuppression was seen, and no drug deaths were reported. Other adverse effects noted included six patients with mild to moderate nausea and vomiting and two patients with nephrotoxicity. One of the cases of nephrotoxicity was recorded as grade 4, indicating severe renal failure, but it is not clear that this effect was drug related as opposed to being a result of progressive neoplasm in the pelvis. Also reported were one case of mild alopecia and one case of severe fatigue.

Cisplatin Therapy

Patient characteristics.—A total of 26 patients were entered onto study to receive cisplatin (table 2). Three were ruled ineligible for study: one because of a primary site of origin other than cervix, another because of lack of documented tumor, and a third because of a GOG performance status of 4. An additional two patients were ruled inevaluable, one because she was never treated and another because insufficient data were submitted to permit evaluation of her case. Of the 21 remaining patients, one was not evaluable for response because there was no measurable lesion. Thus, 20 patients were fully evaluable for response. Among the 20 evaluable patients, histologies were as follows: adenocarcinoma (12 patients); adenosquamous carcinoma (five); clear cell carcinoma (one); and carcinoma not otherwise specified (two). Disease was confined to the pelvis in 11 of the patients, while nine had metastatic disease to extrapelvic sites, with the lung being the most common. Sixteen of the patients had a GOG performance grade of at least 2 (Karnofsky, 50% or better). Fourteen of the 20 had undergone previous surgical therapy, and ten had received prior radiotherapy. Only three had been given hormonal therapy for their neoplasms, and two had received previous chemotherapy.

TABLE 2.—Characteristics of the 26 patients registered to receive cisplatin

Characteristic	No. of patients (%)
Total	26
Ineligible	3
Inevaluable	3
Performance status	
0–2 (Karnofsky, 50%–100%)	16
3 (Karnofsky, 30%–40%)	4
Disease site	
Pelvis only	11
Extrapelvic	9
Histology	
Adenocarcinoma	12
Adenosquamous carcinoma	5
Clear cell carcinoma	1
Carcinoma not otherwise specified	2
Prior therapy	
Surgery	14
Radiotherapy	18
Hormonal therapy	3
Chemotherapy	2
Response	
Complete	1 (5)
Partial	3 (15)
Stable disease	8 (40)
Increasing disease	8 (40)
Adverse effects*	
Leukopenia	7
Thrombocytopenia	3
Nausea and vomiting	17
Azotemia	9
Other	4

*21 evaluable patients.

Response.—Of the 20 patients, one (5%) achieved a complete response, three (15%) achieved partial response, eight (40%) had stable disease, and eight (40%) had increasing disease. Among 12 patients with adenocarcinoma, three responses were seen (one complete and two partial). For the five patients with adenosquamous carcinoma, one partial response was observed. Among the other three patients, no responses were observed. The single complete response lasted 6.3 months with a survival of 11 months, while the median duration of the partial responses was 4 months (range, 1.7–4.3) with a median survival of 7+ months (range, 6.2–9.1). The overall median survival of the 20 patients was 7.3+ months (range, 1.8–29.0). It should be noted that three of the four responses were observed in patients with extrapelvic disease as the measurable disease.

Adverse effects.—Seventeen of the 21 patients (81%) evaluable for adverse effects experienced nausea and vomiting (two mild, 14 moderate, and one severe). Nine of the 21 (43%) developed azotemia; seven had a mild degree, and two had a moderate degree (none had BUN > 60 mg/dl and creatinine > 4 mg/dl). Seven manifested myelosuppression, all seven with leukopenia (four grade 1, two grade 2, and one grade 3) and three with thrombocytopenia (two grade 1 and one grade 2). The lowest recorded wbc count was 1600/μl; the lowest platelet count was 71,000/μl. Other adverse effects reported included moderate alopecia (one patient), mild to moderate fever [two (unrelated to myelosuppression)], and mild paresthesias (one). In no instance was life-threatening toxicity noted, and no drug-related deaths were reported.

DISCUSSION

Cancer of the uterine cervix remains one of the three most common invasive neoplasms of the female genital tract. The vast majority of these neoplasms will be squamous cell carcinoma of the cervix, with $< 15\%$ accounted for by other histologic types. In series of

patients with cervix cancer treated with chemotherapy, these other histologic types have, for the most part, been included as a minor group among the large population of mostly squamous cell carcinomas. In an effort to determine whether these neoplasms respond to systemic therapy differently from squamous cell carcinomas, the GOG phase II trials were designed to evaluate these patients separately.

Piperazinedione and cisplatin were chosen as the first two drugs to be tested. Piperazinedione, a piperazine derivative produced from the fermentation products of a *Streptomyces* species (4), demonstrated some evidence of activity in a variety of adenocarcinomas (5) and was selected for this trial on that basis. Cisplatin, a heavy metal complex, had previously been shown to have a broad spectrum of activity including activity against ovarian carcinoma and squamous cell carcinomas of the cervix (6) and, hence, was selected for study.

The relative infrequency with which these neoplasms are seen makes an adequate evaluation of each specific histologic subtype not feasible. These data do indicate, however, that both drugs possess a moderate activity against these less common types of cervix cancer. The level of activity observed for cisplatin is similar to that reported with use of the same drug in patients with squamous cell carcinoma of the cervix (7) in a larger GOG study.

Adverse effects observed in these trials were similar to those observed in other series using these two drugs (3,7–11) and were tolerable, with no life-threatening problems.

Current GOG plans are to continue to evaluate new agents in these neoplasms in hopes of identifying several active drugs for use, along with possibly cisplatin, in building logical combination regimens for testing. (Piperazinedione, although apparently moderately active, will not be available for further study.) These additional trials may also shed further light on the question of whether these less common histologic types of cervix cancer respond differently from squamous cell carcinomas to systemic therapy.

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Extensive Non-Small Cell Lung Cancer Treated With Mitomycin, Cisplatin, and Vindesine (MiPE): A Southwest Oncology Group Study[1,2,3]

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Ninety-seven previously untreated patients with metastatic non-small cell lung cancer were treated with combination chemotherapy consisting of mitomycin (10 mg/m^2) on Day 1, cisplatin (50 mg/m^2) on Days 1 and 22, and vindesine (3 mg/m^2) on Days 1 and 22 (MiPE). MiPE was repeated at 6-week intervals until disease progression or unacceptable toxicity. The overall response rate was 33%. There were seven complete responses (7%) and 25 partial responses (26%). The median progression-free interval for responding patients was 7 months. Median survival for all patients was 5 months, with 16% surviving 1 year. One patient died from sepsis while neutropenic. The results with MiPE treatment for patients with non-small cell lung cancer compare favorably to other mitomycin-vinca combinations previously tested in the Southwest Oncology Group. [Cancer Treat Rep 70:1101-1104, 1986]

A series of pilot studies has been conducted within the Southwest Oncology Group (SWOG) to investigate the activity of mitomycin-vinca alkaloid-containing combinations in patients with metastatic non-small cell lung cancer (NSCLC). Our initial pilot study, a combination of 5-fluorouracil, vincristine, and mitomycin (FOMi), was reported to have a 41% response rate in 56 patients with advanced NSCLC (1). Subsequently, the activity of full-dose FOMi was determined to be 26% in 127 patients in a group-wide randomized SWOG trial (2). Since that initial study, vindesine has been shown to have activity in NSCLC, with an overall response rate of 16% established in 12 phase II studies involving 330 patients (3). Vindesine was subsequently substituted for vincristine in the FOMi regimen to create the FEMi combination, which resulted in a 21% response rate in 63 patients with stage IIIM1 NSCLC in a SWOG phase II trial (4).

After Mason and Catalano (5) demonstrated activity with the combination of mitomycin, vinblastine, and cisplatin, the SWOG conducted two additional pilot studies with mitomycin-vinca combinations. Mitomycin and vinblastine (VeMi) were tested in 45 patients, giving a response rate of 24% (6). The current study reports the results of the combination of mitomycin, cisplatin, and vindesine (MiPE) in 97 patients with stage IIIM1-extensive NSCLC.

PATIENTS AND METHODS

Between October 1981 and January 1983, 97 patients were treated with MiPE. Patients had biopsy-proven NSCLC based on the original institution diagnosis. All patients had documented distant metastases and were consequently stage IIIM1-extensive based on criteria of the American Joint Committee on Cancer and the Veterans Administration Lung Cancer Study Group (7,8). Patients were previously untreated with chemotherapy, had measurable disease to gauge response, and had normal renal function. Treatment with MiPE consisted of mitomycin (10 mg/m^2 iv) on Day 1; cisplatin (50 mg/m^2 iv) on Days 1 and 22; and vindesine (3.0 mg/m^2 iv) on Days 1 and 22. Courses of treatment were repeated every 42 days until there was objective evidence of tumor progression or unacceptable toxicity. The initial dose of mitomycin was reduced by 25% and the initial dose of vindesine was reduced by 33% for patients $\geq$ 65 years of age. Additional dose adjustments were made for myelosuppression based on peripheral blood cell counts obtained on the day treatment was due. Concomitant radiotherapy to the brain (seven patients) and to bone (six patients) to relieve pain was permitted.

All patients are included in the analyses of response and survival. Response was assessed every 3 weeks at

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[3] Vindesine (Eldesine) was supplied by Eli Lilly and Co.

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the time of scheduled chemotherapy by repeating initially abnormal studies. Complete response (CR) was defined as complete disappearance of all measurable lesions. Partial response (PR) was defined as a 50% reduction in the sum of the products of the two longest perpendicular diameters of all measurable lesions. Progressive disease was defined as any objective increase in tumor dimensions. Deaths which occurred prior to response evaluation were considered treatment failures (four patients). Comparisons of response rates were made using the chi-square test (9). The progression-free interval for responding patients was calculated from the time of starting treatment with MiPE until progressive disease was documented. Survival was calculated from the time of beginning treatment with MiPE until death or until the date of last follow-up using the actuarial method of Kaplan and Meier (10). Comparisons of survival were made using the log-rank test (11). Toxicity of treatment was graded according to SWOG criteria.

RESULTS

The clinical characteristics and results of treatment are summarized in table 1. Ninety-seven patients received 224 courses of MiPE (6 weeks: range, 1-7; median, 2). There were 73 males (76%) and 24 females (24%), ranging in age from 40 to 91 years (median, 63). There were 25 PRs (26%) and seven CRs (7%), for an overall response rate of 33%. The difference in response rates by histology was not significant ($P = 0.403$), but patients classified as having adenocarcinoma had the highest response rate (42%). The most important factor predicting response was performance status. Forty-five percent of patients having a Karnofsky score of 80%-100% responded, whereas only 10% of patients having a Karnofsky score < 60% responded ($P = 0.031$). Pretreatment weight loss and age did not significantly predict response to MiPE. Differences in the CR rate were not significantly different based on histology ($P = 0.452$) or performance status ($P = 0.118$). The median duration of response, measured as the progression-free interval for responding patients, was 6 months. The median duration of response for PRs was 5 months and for CRs was 8 months.

Ninety-two of 97 patients (95%) treated with MiPE have died. The overall median survival was 6 months (table 1). Six patients survived > 2 years and five are still alive from 24 to 30 months. Two of the five patients surviving > 2 years remain free of disease. These five long-term survivors had high pretreatment performance scores (four of five had scores ≥ 80%) and CRs with MiPE (four of five patients). Significant differences in overall survival were observed for several pretreatment clinical characteristics including histology (large cell undifferentiated carcinoma worse than adenocarcinoma, $P < 0.001$; and squamous cell cancer, $P = 0.02$), performance status (comparisons of all groups in table 1, $P < 0.01$), and weight loss (≥ 10% weight loss worse than no weight loss, $P = 0.025$).

The common side effects of treatment were nausea and vomiting (table 2). Vomiting was usually controlled within 24 hours of treatment, but was prolonged in 11% of patients. Myelosuppression was the only cause of serious toxicity. Neutropenia and fever were seen in three patients, and one of these patients died as a result of treatment with MiPE. In general, myelosuppression with MiPE was modest and only 12% of patients had leukocyte counts < 3000/μl on the day of therapy. Three patients developed moderate to severe dyspnea and radiographic findings compatible with pulmonary fibrosis

TABLE 1.—Patient characteristics and results of treatment with MiPE

Characteristic	No. of patients	Overall response rate (%)	No. of responses (%)		Survival	
			PR	CR	Median (mos)	% 1-year
Histology						
All NSCLC	97	33	25 (26)	7 (7)	5	16.0
Adenocarcinoma	43	42	13 (30)	5 (12)	6	23.2
Large cell	9	22	2 (22)	0	3	0.0
Squamous cell	40	28	9 (22)	2 (5)	4	15.0
Others	5	20	1 (20)	0	8	20.0
Performance status						
80%-100%	47	45	15 (32)	6 (13)	8	29.8
60%-70%	40	25	9 (22)	1 (2)	4	7.5
< 60%	10	10	1 (10)	0	2.5	0.0
Initial weight loss						
None	35	37	9 (26)	4 (11)	8	20.0
< 10%	19	32	5 (26)	1 (5)	5	26.3
≥ 10%	43	30	11 (26)	2 (5)	4	11.9
Age (yrs)						
≤ 65	69	33	18 (26)	5 (7)	5.5	22.9
> 65	28	32	7 (25)	2 (7)	6	3.7

TABLE 2.—Toxic effects of treatment with MiPE

Toxic effect	Frequency by grade (%)			
	Moderate	Severe	Life-threatening	Fatal
Thrombocytopenia	3	1	0	0
Anemia	11	0	0	0
Leukopenia	8	1	2	1
Peripheral neuropathy	0	1	0	0
Vomiting	15	11	0	0
Skin necrosis	1	1	0	0
Increased creatinine	6	0	0	0
Clinical lung fibrosis	1	2	0	0

presumably due to mitomycin. However, histologic proof of fibrosis was not obtained, and the symptoms either stabilized or resolved after discontinuing the drug.

DISCUSSION

Our results indicate that the MiPE combination has objective activity in NSCLC as gauged by tumor response. Based on an analysis of recognized pretreatment prognostic factors, a group of patients could be identified with a higher probability of response to MiPE. Patients who were still able to carry out normal activity (Karnofsky score of 80%–100%) had an objective response rate of 45% and a CR rate of 13%. MiPE had relatively little activity in patients with lower performance scores. Only one of 50 patients with a Karnofsky score $< 80\%$ had a CR.

Table 3 summarizes the results of five consecutive phase II–III SWOG trials of NSCLC conducted between 1979 and 1984. The results with MiPE compare favorably with our previous experiences using mitomycin-vinca alkaloid combinations in patients with NSCLC. The CR rate of 7% and the response duration of 6 months suggest that MiPE could be considered for future randomized phase III trials in NSCLC.

Other groups have shown evidence of objective antitumor activity of mitomycin, cisplatin, and vinca combinations in phase II trials (5,12–14). Response rates have been relatively consistent, varying between 25% and 53%. CRs have varied between 2% and 5%. However, it is not possible to determine whether this apparent consistency in phase II trials indicates some modest advance in treatment of NSCLC, or simply improved patient selection. Randomized trials with appropriate stratification for prognostic factors are needed. Early results from two randomized trials are currently available. Ruckdeschel et al (15) have evaluated several regimens in a prospective randomized Eastern Cooperative Oncology Group (ECOG) trial, including MVP (mitomycin, vinblastine, and cisplatin). In that ECOG trial, MVP had a 26% response rate (5% CRs) in 104 patients. The majority of patients had an ECOG performance score of 0–1 (Karnofsky equivalent $\geq 80\%$). Einhorn et al (16) reported a lower response rate of 16% in 34 patients randomized to receive a combination of mitomycin, cisplatin, and vindesine. However, the median Karnofsky performance score in this study was 70%. Given the overwhelming influence of small changes in performance status on response rates, the differences between these studies may not be significant.

It is unknown whether a three-drug mitomycin-vinca-cisplatin combination offers any advantage over a two-drug cisplatin-vinca combination. The results of numerous phase II trials demonstrate remarkably similar results as gauged by response rates. In a recent review summarizing available clinical trials through 1983, the response rate of mitomycin-vinca-cisplatin combinations was 37% in 235 patients and the response rate of vinca-cisplatin combinations was 40% in 343 patients (3). Previously, the Memorial Sloan-Kettering group (17) added doxorubicin and cyclophosphamide to cisplatin and vindesine in an attempt to improve on the 43% response rate seen with cisplatin and vindesine. To prevent excessive myelosuppression, the dose rates of doxorubicin and cyclophosphamide were reduced by 25% from those initially reported to be effective by Eagan et al (18) in the CAP regimen (cyclophosphamide, doxorubicin, and cisplatin), and the dose rate of vindesine over the first 6 weeks of treatment was reduced 33% from that initially reported by Gralla et al (19) in the vindesine-cisplatin regimen. The result was a decrease in the response rate to 24% for the new four-drug regimen. In the current study, the dose rate of vindesine (3 mg/m^2 every 21 days) represents only 33% of the dose administered by Gralla et al over the first 6 weeks of treatment. The dose

TABLE 3.—Mitomycin-vinca combinations in non-small cell lung cancer: comparisons of SWOG phase II–III results*

Regimen (ref No.)	No. of patients	Response rates (%)				Progression-free interval (mos)	Median survival (mos), PS $\geq$ 70%
		All patients		PS $\geq$ 70%			
		CR + PR	CR	CR + PR			
FOMi (1)	56	41	7	48		5	5
FOMi (2)	127	26	3	33		4	5
FEMi (4)	63	21	5	29		4	6
VeMi (6)	45	24	0	—		4	—
MiPE	97	33	7	41		6	7

*PS = performance status.

rate of vindesine was reduced to accommodate the expected myelosuppression from mitomycin and may have been unnecessarily excessive, since only 12% of patients had documented leukocyte counts $< 3000/\mu l$. Kris et al (21) were able to add mitomycin to a vindesine-cisplatin combination, giving vindesine at a rate of 3 mg/m^2 each week for 6 consecutive weeks without excessive toxicity. However, Einhorn et al (16) reported excessive toxicity while attempting to administer an identical combination using the same dose schedule as Kris et al.

The effect of cisplatin dose rate on survival and duration of response for patients with NSCLC is not clear. Gralla et al (19) have previously demonstrated that 120 mg/m^2 of cisplatin (given on Days 1, 29, and every 6 weeks thereafter, or 360 mg/m^2 during the first 12 weeks of treatment) resulted in a longer remission duration and survival for responding patients compared to 60 mg/m^2 of cisplatin (same schedule). Klastersky et al (20) were not able to show any significant advantage for high-dose cisplatin (120 mg/m^2) compared to low-dose cisplatin (60 mg/m^2) when combined with etoposide. In the current study, cisplatin was administered every 3 weeks at 50 mg/m^2 (200 mg/m^2 during the first 12 weeks of treatment), a dose rate nearly identical to the "low-rate" schedules of the previous randomized trials.

The results of the current study and those of others indicate that cisplatin-vinca combinations with or without mitomycin have significant antitumor activity in patients with NSCLC who have a high pretreatment performance status (Karnofsky score $\geq$ 80%) (22). The current regimen and similar combinations have very little activity in patients with poor performance status (Karnofsky score $<$ 70%). Currently, randomized trials are probably needed to determine if the addition of mitomycin to a cisplatin-vinca combination increases the response rate without causing excessive toxicity. Finally, randomized trials comparing a vinca-cisplatin regimen with or without mitomycin to supportive care alone are indicated before these regimens are used in routine clinical practice.

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Therapeutic Response in Phase I Trials of Antineoplastic Agents[1]

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We analyzed the therapeutic effect reported in 187 phase I trials of 54 anticancer drugs introduced into National Cancer Institute-sponsored clinical trial from 1974 to 1982. An additional 12 drugs entering clinical trial prior to 1974 were also examined. Objective responses (partial and complete) were reported in 271 of the 6447 patients (4.2%). Thirty-nine percent of the patients were treated at an initial dose level greater than or equal to the dose ultimately recommended for phase II trials. Patients in phase I trials generally had adequate performance status (Karnofsky scale > 80% or Eastern Cooperative Oncology Group 0, 1, or 2). More than 90% of the patients had received prior chemotherapy. We next examined the therapeutic effect observed in phase II trials for each of the drugs. Thirty-eight of the 54 drugs had completed at least one phase II trial. Twenty-one drugs were rated active, and nine were rated inactive. For the drugs entering clinical trial since 1974, the median phase I response rate for those active in phase II was 4.3%, compared to 2.7% for the drugs not found active in phase II. This difference was not statistically significant. The tabulated response rate in phase I trials reported here should be interpreted cautiously. There are many factors which may contribute to significant variability in the reported response rates, including the heterogeneity of patient population with respect to prior therapy and tumor type, lack of requirement for measurable/evaluable disease on entry into many studies, and variations in the rigor with which tumor sites are followed for response. These factors may lead to either an overestimate or underestimate of the true response rate in phase I. Although little therapeutic effect is produced in phase I, we discuss several measures which might increase patient benefit during these trials. [Cancer Treat Rep 70:1105–1115, 1986]

Phase I trials of antineoplastic agents are conducted with therapeutic intent. Although it is widely conceded that antitumor effect is rarely achieved, there are no published studies which document this. Responses in phase I are often cited as part of the rationale for a specific phase II study. Conversely, drugs may be removed from further clinical trial after phase I studies because of lack of response in phase I. However, we are unaware of correlations between therapeutic results observed in phase I with those observed in phase II that might lend support for these practices. We undertook the present work to attempt such correlations, to delineate phase I response rates, and to describe certain general features of phase I studies.

MATERIALS AND METHODS

Phase I Trials

We selected drugs for this study in two groups:

(1) All 42 cytotoxic drugs entered clinical trial under National Cancer Institute (NCI) sponsorship between 1974 and 1982.—Data for these drugs came from either (*a*) the Clinical Trials Monitoring Service (CTMS) of the NCI, which since 1980 has served as repository for all patient case report forms on NCI-sponsored phase I trials (data on 15 of the 42 drugs were derived from this data base); or (*b*) the published literature if the drug entered clinical trials before 1980 (Bibliography). In the few instances where a particular study had not been monitored by CTMS or conducted under NCI sponsorship, the published literature was also the source of the data.

(2) An additional 12 drugs entering clinical trial before 1974.—Data for these drugs were also derived from the published literature (Bibliography).

From the list of studies identified by this process, we selected all those phase I studies of single agents which (*a*) involved adults; (*b*) included patients with three or more tumor types; and (*c*) involved systematic dose finding (at least three dose levels explored) in attempting to define a tolerated phase II dose.

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For each selected study we recorded the following about the patients: (*a*) number entered; (*b*) performance status; (*c*) percent with prior cytotoxic therapy; (*d*) number of patients at each dose level on the first course of therapy; (*e*) diagnoses; and (*f*) antitumor response, according to the criteria reported by the investigator. We also recorded the recommended dose for subsequent phase II studies.

A total of 54 drugs involving 187 phase I trials were analyzed for this paper. The literature review was the source of information for 70% of the total patient data base and for 60% of the drugs tested between 1974 and 1982.

Phase II Trials

Only single-agent phase II results are included in the data base. The data are derived from both the published literature and unpublished reports. Data from the former are abstracted from the original publication of a phase II trial; the sources for the latter include progress reports submitted to the NCI, and minutes of the clinical cooperative groups. All abstracting is performed by a professional abstractor and has been spot-checked for accuracy by the authors. The responses are tabulated according to the criteria of the investigator.

An overall response rate for each drug in each tumor type was calculated by pooling the numerators (number of partial and complete responders) and the denominators (the number of patients evaluable for response) from all studies reporting data on that tumor type. For leukemia trials only complete remissions were included. If there were fewer than 14 evaluable patients in the pooled denominator, then a drug was rated inevaluable in that tumor type.

Drug Activity Rating

For each response rate an exact two-sided 80% confidence bound was calculated. Using this information, the drug's activity rating for each tumor type was assigned in the following way. *Active*—If the lower bound of the 80% confidence interval was $> 10\%$, the drug was scored as active. *Inactive*—If the above condition was not fulfilled but the upper bound of the 80% confidence interval was $< 15\%$, the drug was scored as inactive. *Indeterminate*—If neither of the above conditions was fulfilled, then the drug activity in that tumor type was rated as indeterminate. The formal possibility that both of these criteria might be satisfied could not occur since the tests are applied sequentially.

Overall Activity Rating

A drug was assigned an overall clinical activity rating. An active rating is given if the drug is scored as active in at least one tumor type. To define a drug as overall inactive that drug had to be rated negative in at least leukemia or lymphomas and at least one solid tumor. If the drug met neither of these tests, its overall activity was rated as indeterminate.

TABLE 1.—Demographics of phase I studies

	Year drug entered clinical trial		
	1980 and later	1974–1979	Pre-1974
Median No. of patients entered/drug	116	119	105
Median No. of studies/drug	4	3	2
Median No. of patients entered/study	25	30	40

Phase I–II Correlations

We then compared the mean phase I response rates of active versus inactive phase II drugs using the Wilcoxon rank-sum test (two-tailed). This test was applied only to the drugs entering clinical trial since 1974, since no selection factors were applied to these drugs other than the fact of entering clinical trial under NCI sponsorship.

RESULTS

We compared the drugs in three groupings according to the time of introduction into clinical trial: (*a*) 1980–1982; (*b*) 1974–1979; and (*c*) pre-1974.

Demographics

For each drug the total number of patients entered in phase I studies ranged from < 10 to > 300 (median, 116 patients). Thirty percent of the drugs were evaluated in > 150 patients and 17% were evaluated in > 200 patients.

Table 1 shows that the median total patients entered in all phase I trials for each drug is nearly the same in the three time periods. Similarly, wide ranges in patient numbers occur in all time intervals. The number of studies per drug has tended to increase with time, with a corresponding decrease in the number of patients entered in a particular study.

Performance status.—Information on performance status of phase I patients was generally unavailable from the published literature. By contrast, CTMS records contained this information in 92% of patient (1761 of 1921) records. Nearly half of the patients had a performance status (PS) of 0 or 1, and almost 80% were 0, 1, or 2 (PS 0, 8%; PS 1, 39%; PS 2, 31%; PS 3, 16%; and PS 4, 6%).

Prior chemotherapy.—Information on prior chemotherapy is also very incomplete in the published literature, particularly for the studies before 1974. The great majority of patients for whom information is available since 1974 have had prior chemotherapy. Since 1980, in only three tumors (hypernephroma, pancreatic cancer, and carcinoma of unknown primary) have $> 10\%$ of the patients not received previous chemotherapy (table 2).

First-course dose.—We examined the initial dose received by each patient as a percent of the recommended phase II dose for that drug (table 3). In the last 10 years, about 40% of patients have received a first-course dose greater than or equal to the recommended phase II

TABLE 2.—Prior chemotherapy status of phase I patients

	Year drug entered clinical trial		
	1980–1982	1974–1979	Pre-1974
No. of patients entered	2370	2480	1597
No. of patients for whom information was available	2252 (95%)	1476 (59.5%)	209 (16.8%)
No. with prior chemotherapy	2118 (94%)	1307 (89%)	133 (49%)

dose. As before, the published literature often fails to record these data.

Diagnosis.—In the last 5 years, about 20% of the patients have had tumor types often regarded as "sensitive" [leukemia, lymphoma, small cell lung cancer, and breast cancer (table 4)]. Since histological breakdown of lung cancer is generally unavailable in the published literature, we are able to make only approximate comparisons with earlier periods. These show, however, that the percent of patients with either leukemia, lymphoma, or breast cancer is about the same in all three periods. Individual drugs varied greatly in the distribution of the various cancer diagnoses. For example, $> 40\%$ and $> 60\%$ of those patients given vincristine and pentostatin, respectively, had lymphoma or leukemia. On the other hand, $< 1\%$ of patients receiving IMPY, acivicin, hycanthone, pentamethylmelamine, ICRF-187, razoxane, indicine, fluorodopan, zorubicin, bisantrene, aminothiodiazole, or dianhydrogalactitol had these malignancies.

Survival.—Fifteen percent of the 1921 patients monitored by the CTMS died during the course of a phase I study. Seventeen percent have been withdrawn from or refused to continue to participate in the trial. The remaining 68% completed phase I studies. Fifty-three percent of the 1921 patients received one course of a phase I drug, 26% received two courses, and the remaining 21% received three or more courses. Similar information is not uniformly available in the published literature.

TABLE 3.—1st course dose given phase I patients

	Year drug entered clinical trial		
	1980–1982	1974–1979	Pre-1974
No. of patients entered	2370	2480	1597
No. of patients for whom information was available	2280 (96.2%)	1003 (40.4%)	297 (18.6%)
No. in whom 1st course dose was ≥ recommended phase II dose	874 (38%)	417 (42%)	115 (38%)

TABLE 4.—Diagnoses of patients involved in phase I studies

	Year drug entered clinical trial		
	1980–1982	1974–1979	Pre-1974
No. of patients entered	2370	2480	1597
No. of patients for whom information was available	2340	2239	1350
Disease			
Lung cancer	358 (15%)	471 (21%)	252 (19%)
Colon cancer	513 (22%)	465 (21%)	107 (8%)
Melanoma	133 (6%)	208 (9%)	171 (13%)
Breast cancer	203 (9%)	175 (8%)	68 (5%)
Sarcoma	147 (6%)	133 (6%)	78 (6%)
Kidney cancer	137 (6%)	109 (5%)	49 (4%)
Head and neck cancer	135 (6%)	83 (4%)	129 (10%)
Unknown primary	86 (4%)	94 (4%)	43 (3%)
Lymphoma	97 (4%)	50 (2%)	118 (9%)
Leukemia	97 (4%)	106 (5%)	57 (4%)

Phase I Response Rates

Table 5 shows objective response rates for each drug. Partial response (PR) and complete response (CR) are summed across all phase I studies. Table 6 shows the totaled response rate for all drugs, tabulated by time period. Although overall response rates are low, the observed rates vary widely for individual drugs, ranging from 40% for vincristine to 0% for several more recent drugs.

For the response rate analysis, we included all entered patients in the denominator. We were unable to limit the denominator to those evaluable for tumor response, as is usual in phase II studies, because published reports of phase I trials rarely define evaluability for response. Among the 1921 patients monitored by CTMS, 719 had measurable disease. Among these patients, investigators reported five CRs (0.7%), 16 PRs (2.2%), and 28 minor responses (3.9%). The 2.9% objective response rate for the subset with measurable disease was similar to the 2.3% objective response rate for the whole cohort from 1980 to 1982.

Table 7 examines therapeutic results according to cancer diagnosis. During the pre-1974 period, patients with lymphoma, testicular cancer, and breast cancer had relatively high response rates, almost certainly because active agents from the pre-1974 period were selected for this analysis. During the past 10 years, response rates in hematologic cancers are greater than those in solid tumors. Results in those solid tumors commonly thought of as responsive (eg, ovary, breast, and testis) have been very similar to those in solid tumors commonly considered resistant. Among 43 pa-

TABLE 5.—Phase I: Drugs, patients, and response rates

Year of IND submission	Drug	No. of — Studies	No. of — Patients	Response rate (%)*
1959	5-Fluorouracil	2	230	4.3
1963	Vincristine	1	40	40.0
1965	Carmustine	1	144	11.8
1971	Mitolactol	3	202	9.9
	Cisplatin	5	187	8.6
	Ifosfamide	2	72	8.3
	5-Azacitidine	2	55	20.0
	Semustine	4	167	10.8
1972	Etoposide	2	95	9.5
	Bleomycin	1	59	15.3
1973	Piperazinedione	2	115	2.6
	Gallium nitrate	4	149	2.7
1974	Dianhydrogalactitol	4	136	5.1
	Zinostatin	3	211	5.7
1975	Anguidine	4	122	0.0
	Dichlorylallyl lawsone	1	25	0.0
	Aminothiadiazole	1	36	5.6
	Maytansine	5	237	2.5
	Hycanthone	2	27	0.0
	Pyrazofurin	3	111	2.7
1976	Chlorozotocin	5	155	5.2
	Fluorodopan	1	39	12.8
	Zorubicin	1	9	11.1
	3-Deazauridine	1	19	5.3
1977	Bruceantin	3	114	0.0
	Amsacrine	5	190	4.2
	Indicine *N*-oxide	3	123	3.2
	PALA	6	223	1.3
	IMPY	4	114	0.0
1978	L-Alanosine	3	116	0.0
	ICRF-187	4	119	2.5
	PCNU	5	199	6.5
	Pentamethylmelamine	8	216	0.5
1979	DON	4	106	0.0
	Diaziquone	7	259	3.1
	Mitoxantrone	9	305	4.3
	Acivicin	6	146	0.0
	Pentostatin	4	93	11.8
	Aclarubicin	6	134	1.5
1980	5-Methylterahydrofolate	1	9	0.0
1981	Bisantrene	5	133	7.5
	Spirogermanium	3	116	2.6
	Teroxirone	2	111	0.0
	5-Dihydroazacitidine	3	65	0.0
	Carboplatin	5	155	1.9
	Echinomycin	3	76	0.0
	6-Methylmercaptopurine riboside	1	4	0.0
	Triciribine phosphate	5	121	0.0
	Homoharringtonine	6	191	0.5
1982	*N*-Methylformamide	3	74	0.0
	Fludarabine	3	77	0.0
	Tiazofurin†	7	67	0.0
	Acodazole†	2	11	0.0
	Spiromustine†	4	52	0.0

*Response rate = CR + PR/patients entered.
†Phase I studies ongoing.

tients with small cell lung cancer monitored by CTMS, there was one PR.

Phase II Activity

Thirty-eight of the 54 phase I drugs have completed at least one phase II trial. We rated 21 of these drugs overall active because of activity in at least one tumor type. Nine of the 38 drugs were rated inactive and eight were rated indeterminate, usually because there was no adequate phase II trial in a hematologic malignancy (table 8). Sixteen of the total of 56 drugs have not completed at least one phase II trial (table 9). Trials are in progress or planned for nine of these compounds whereas seven did not enter phase II trial, primarily because of unacceptable toxicity in phase I. Considering only the period 1974 and later (ie, the period in which we have examined all compounds entering NCI-sponsored phase I trials), there are nine active agents (aclarubicin, amsacrine, diaziquone, bisantrene, carboplatin, chlorozotocin, mitoxantrone, pentostatin, and zorubicin); nine inactive agents; eight indeterminate agents; nine agents with phase II trials ongoing or planned; and seven agents which did not enter phase II trial (tables 8 and 9).

Among the five drugs with evaluable phase II data that produced no objective responses in phase I (bruceantin, anguidine, acivicin, DON, and L-alanosine), none was rated as active in phase II. Anguidine and L-alanosine were scored as inactive in phase II after testing in nine and four tumor types, respectively, including both leukemia and solid tumors. DON, acivicin, and bruceantin scored as inevaluable, since none had been tested in hematologic tumors. Dichlorylallyl lawsone, hycanthone, and IMPY showed no responses in phase I but were not tested in phase II.

Phase I–II Correlations

We correlated phase I response rates with phase II activity for the post-1974 drugs. The median overall phase I response rate for active phase II drugs was 4.3% (range, 1.5%–11.8%), compared to 2.7% (range, 0%–5.7%) for inactive phase II drugs ($P = 0.16$) (fig 1).

DISCUSSION

The present study demonstrates a low probability of therapeutic benefit during a phase I trial. This finding confirms a common clinical impression of many investigators.

Numerous factors confound phase I and II response rate data. Several factors could skew the reported response rates of drugs independent of a drug's true activity. Those factors which pertain to phase I trials include: (*a*) including all patients entered in the denominator, rather than limiting the calculation to those with measurable disease; (*b*) variations in assessment of antitumor effect; and (*c*) variations in patient characteristics, including tumor type, extent of prior therapy, and performance status.

TABLE 6.—Therapeutic results in phase I studies

	Year drug entered clinical trial			
	1980–1982	1974–1979	Pre-1974	Total
No. of patients entered	2370	2480	1597	6447
Response				
CR	10 (0.4%)	4 (0.2%)	29 (1.8%)	43 (0.7%)
PR	45 (1.9%)	71 (2.9%)	112 (7.0%)	228 (3.5%)

Precise determination of phase I response rates was hampered because the denominator consisted of all entered patients rather than patients with measurable tumor, which is not a general requirement for entry in a phase I study. Since by definition an objective response cannot occur in patients without measurable disease, inclusion of such patients could result in an underestimate of the response rate which might have been observed in a population of patients with measurable disease.

Information on the number of patients with measurable tumor was, as a rule, unavailable in the published literature. This information is more readily available for the post-1980 period, since our data source for these trials was primarily individual patient forms submitted to CTMS rather than literature. We examined 1719 of the 1921 patients monitored by CTMS recorded as having measurable lesions. The response rate in this subset was similar to that of the whole cohort. However, there is no assurance that this is a representative sample of the measurable patient group. Hence, the actual phase I response rate may not correspond to the rates we have shown.

A second reason for variation in reported response rates is that since phase I protocols often do not specify tumor assessment as a routine measurement, investigators may not follow tumor size as rigorously in phase I trials as in phase II trials nor apply standard criteria for evaluating them. Lack of adequate attention to response assessment might result in either an overestimate or an underestimate of the true response rate.

A third factor contributing to variation in response rates is heterogeneity of patient characteristics. Since most of the drugs active in phase II are found to be so in hematologic malignancies, the proportion of patients with those tumor types may have a profound effect on the therapeutic effect observed in those studies. More than twice as many lymphoma patients (9%) entered phase I trials among the pre-1974 drugs than did among the post-1980 drugs (4%). Similarly, variations in the extent of prior chemotherapy could account for an important component of the variation. Most phase I trials conducted in a given era are probably similar in their patient characteristics. However, these characteristics have changed over time. Moreover, the correlation between phase I and II is impeded because of the dissimilar patient populations.

Further difficulty attaches to the definition of an active and inactive drug following phase II evaluation. In particular, can a drug be considered inactive if it has been tested only in tumors highly unlikely to respond to any drug? A case can certainly be made for a negative answer. On the other hand, there is no assurance that, by the time a given phase II drug is administered, a breast cancer patient is any more favorable than a colon patient. In fact, phase I response rates were similar for

TABLE 7.—Therapeutic results by disease site*

	Year drug entered clinical trial					
	1980–1982		1974–1979		Pre-1974	
Disease	Entered	CR + PR (%)	Entered	CR + PR (%)	Entered	CR + PR (%)
Leukemia	97	8 (8.2)	106	5 (4.7)	57	2 (3.5)
Lymphoma	97	6 (6.2)	50	7 (14)	118	39 (33)
Lung cancer	358	4 (1.1)	471	10 (2.1)	252	8 (3.2)
Colon cancer	513	5 (1.0)	465	10 (2.2)	107	4 (3.7)
Melanoma	133	6 (4.5)	208	8 (3.8)	171	13 (7.6)
Breast cancer	203	1 (0.5)	175	2 (1.1)	68	19 (27.9)
Sarcoma	147	0 (0)	133	5 (3.8)	78	4 (5.1)
Kidney cancer	137	4 (2.9)	109	4 (3.7)	49	5 (1.0)
Head and neck cancer	135	2 (1.5)	83	2 (2.4)	129	12 (9.3)
Unknown primary	86	1 (1.2)	94	2 (2.1)	45	2 (4.4)
Ovary cancer	67	0 (0)	53	0 (0)	30	2 (6.7)
Testis cancer	13	0 (0)	12	0 (0)	33	10 (30.3)

*Unless otherwise indicated, values = No. of patients.

TABLE 8.—Phase II ratings

Drug	Best CR + PR rate (%)	80% confidence limits (%)	Tumor type
Active			
Aclarubicin	21	17–26	Leukemia
Amsacrine	20	14–26	Leukemia
Azacitidine	14	11–16	Leukemia
Carmustine	47	41–53	Central nervous system
Bisantrene	13	10–16	Breast cancer
Bleomycin	30	27–33	Lymphoma
Carboplatin	38	31–45	Ovarian cancer
Chlorozotocin	14	10–19	Lymphoma
Cisplatin	48	45–50	Ovarian cancer
Diaziquone	18	12–27	Lymphoma
Mitolactol	34	30–38	Breast cancer
Etoposide	31	23–40	Testicular cancer
5-Fluorouracil	20	18–22	Colon cancer
Gallium	25	20–31	Lymphoma
Ifosfamide	59	48–70	Lymphoma
Mitoxantrone	17	15–18	Lymphoma
Pentostatin	50	33–67	Lymphoma
Piperazinedione	32	20–47	Lymphoma
Zorubicin	44	40–48	Leukemia
Semustine	25	19–32	Lymphoma
Vincristine	44	30–58	Breast cancer
Indeterminate			
Acivicin			
Bruceantin			
DON			
Fluorodopan			
Homoharringtonine			
ICRF-187			
PCNU			
Spirogermanium			
Negative			
Alanosine			
Anguidine			
Deazauridine			
Dianhydrogalactitol			
Indicine *N*-oxide			
Maytansine			
Zinostatin			
PALA			
Pyrazofurin			

sensitive and resistant solid tumors, although, as noted, hematologic tumors were more likely to respond even in phase I.

The above list of difficulties hampering retrospective analysis of phase I response rates, particularly in connection with subsequent phase II results, indicates why our phase I–II correlations can only be suggestive. Although active drugs had somewhat greater phase I response rates than inactive drugs, there was substantial overlap and the difference was not statistically significant. Those drugs that have become established in routine cancer treatment (pre-1974 drugs) had phase I response rates considerably above average. This shows that in that era active drugs did generally show activity in phase I trials. Those drugs were not included in the correlation analysis, however, because the extent of prior therapy has clearly changed.

While this analysis does not suggest a statistically significant correlation between activity in phase I and II, we asked whether the drugs with no responses in phase I showed activity in phase II. Of the five drugs totally inactive in phase I, none were scored as active following phase II testing. However, three of the five drugs could only be scored as indeterminate because of insufficient numbers treated in phase II. We conclude that the limitations of these data and the small number of drugs examined make it inadvisable to establish a policy of discontinuing the development of drugs that show no responses in phase I.

It might be possible to use responses in specific diseases in phase I to encourage phase II studies of specific tumor types. This procedure would certainly be unsystematic, since the patient mix varies considerably from study to study in phase I. Currently, the relatively common (and resistant) diseases are generally overrepresented compared with the less common and more sensi-

TABLE 9.—Status of phase II trials of drugs not yet evaluable

Trials ongoing or planned
Aminothiadiazole
N-Methylformamide
Fludarabine
Triciribine
DHAC
Echinomycin
Tiazofurin
Acodazole
Spiromustine
No trials
Teroxirone
5-Methyltetrahydrohomofolate
Hycanthone
6-Methylmercaptopurine riboside
Dichlorylallyl lawsone
Pentamethylmelamine
IMPY

tive tumors. Nevertheless, it is difficult operationally to ignore the existence of individual responders in a phase I study and such responders do increase the enthusiasm of investigators for pursuing a drug in phase II.

Is it possible to improve the prospects for therapeutic benefit in phase I trials? Factors responsible for the low response rate could include: (*a*) the extent of prior therapy; (*b*) the extent to which patients are treated at low doses during the early stages of a phase I trial; (*c*) poor PS of phase I patients; (*d*) an overwhelming preponderance of patients with resistant diseases entered in phase I studies; and (*e*) the low inherent activity of the drugs investigated.

Prior therapy.—The demographic analysis suggests a decreasing percentage of untreated patients since the pre-1974 period. Although it is possible that because the pre-1974 drugs were selected for inclusion in this study due to their activity, the higher proportion of previously untreated patients in the pre-1974 drugs is not reflective of the conduct of phase I trials as a whole during this period. However, we do not believe it likely, since the phase I studies on these drugs were conducted before their activity was known. Nevertheless, the analysis of the post-1974 drugs revealed that only rarely have phase I patients not received prior therapy. This reflects the widespread use of chemotherapy during these years. Given the large number of phase II drugs to be tested and the availability of standard therapy for many cancers, this trend is unlikely to reverse.

First-course dose.—Surprisingly, nearly 40% of the patients from 1980 on and slightly > 40% of those in the preceding 5 years received a dose which was greater than or equal to the dose that they would have received if they had participated in a phase II rather than a phase I study of the particular drug. It is probably common to add patients at the highest dose levels to expand the experience at or near the projected phase II dose. We believe this is done to increase the confidence of the recommendation for a phase II dose. Perhaps some of this extra accrual also represents exploration for activity. Finally, a drug may have irregular or patchy toxicity, and escalation may proceed well beyond the ultimately recommended phase II dose before a phase II dose is settled. Opportunities to observe response might be furthered if more rapid dose escalations were feasible.

PS.—About 80% of phase I patients had a PS of 2 or better, which is similar to the general requirement for phase II studies. It seems unlikely, therefore, that PS accounts for the low recorded phase I response rates.

Resistant tumors.—Our data show that, even in phase I trials, leukemias and lymphomas remain the least resistant tumors. There is little distinction in response rates among the various solid tumors, ie, there are no sensitive solid tumors in phase I. Slightly < 10% of phase I patients have leukemia or lymphoma.

There are several possibilities for improvement in therapeutic effect in phase I trials. Most important is drug selection. Although nearly one-third of drugs are active in phase II in some diseases, they are only marginally so, with response rates hovering about 20% in more favorable patient populations than in phase I. Fewer than one in ten of these drugs are eventually incorporated into widespread use in cancer therapeutics.

Since most patients in phase I trials either have intrinsically resistant tumors or have been treated with multiple drugs, it is clear that the prevalence of de novo

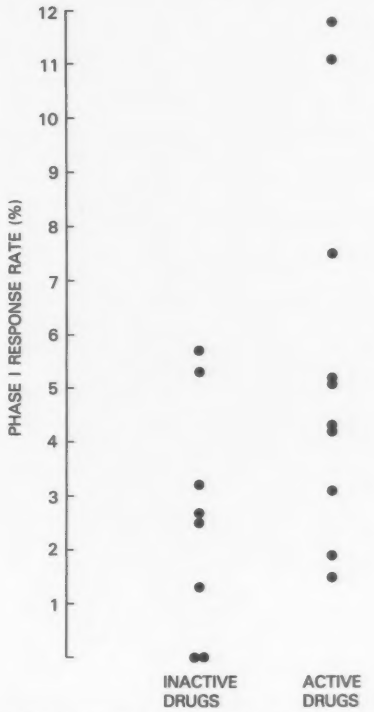

FIGURE 1.—Phase I response rate for each drug according to activity rating in phase II.

or acquired multidrug resistance is very high. A screening process that selects drugs that are not cross-resistant to commonly used drugs might well improve their therapeutic effect in phase I. Changes in progress of the screening program of the Division of Cancer Treatment will ensure that many candidate agents are evaluated against resistant human cell lines.

A more efficient scheme of dose escalation could decrease the 55% of patients treated below the recommended phase II dose. It is doubtful to us that alteration of escalation schemes based solely on mathematical or statistical approaches without a biological basis will be fruitful. One approach recently proposed is to relate dose administered to the blood concentrations and area under the time-concentration curve. The goal is to test whether pharmacokinetic parameters such as concentration and area under the time-concentration curve can be related to clinical toxic and therapeutic effects. If it can be demonstrated that there is a correlation between such pharmacologic endpoints in man and suitable animal species, it may be possible to direct the dose escalations based on pharmacokinetic targets rather than the classic Fibonacci scheme. This concept is now undergoing prospective evaluation.[5]

Schabel et al have recently discussed the striking individual variation of antitumor effect among mice of the same species bearing tumor of identical origin. They propose that this may be due primarily to host variability in drug metabolism.[6] This observation may be very pertinent to the clinical setting. The heterogeneity of therapeutic effect after similar drug dose is usually ascribed to differences in intrinsic drug sensitivity of the tumors. However, it may be that therapeutic effect at any given dose level in a phase I trial may be heavily influenced by the pharmacokinetic behavior of the drug in each individual patient and that such differences in host metabolism contribute to the variability in response. Although detailed data on organ function were not evaluated in this study, it is possible that impaired hepatic or renal function due to prior therapy or tumor may affect tumor response through alteration in drug metabolism. Detailed pharmacokinetic evaluation in each patient in a few carefully selected phase I trials may yield significant insight into this question.

Finally, the use of in vitro assays to select patients whose tumors exhibit sensitivity to the experimental agent is at least theoretically attractive. However, there are no assays currently available which reliably culture the patient's tumor, are practical, are reproducible, and whose predictive value has been validated.

In the future, therapeutic effects occurring during phase I trials may have an increased role in planning phase II trials. The extent of this role can only be established prospectively by investigators (*a*) selecting patients not so extensively pretreated or debilitated that response is almost impossible, (*b*) including more information about prognostic factors in reports of phase I trials, (*c*) evaluating patients for response as systematically as they would in a phase II study, and (*d*) examining the relationship of pharmacologic parameters to therapeutic effect.

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Association of Severe and Fatal Infections and Treatment With Pentostatin[1,2]

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Pentostatin (dCF), an inhibitor of adenosine deaminase, has shown activity in the treatment of several lymphoid malignancies, even in the earliest phase I trials. An analysis of the first 300 patients treated in such trials shows a high incidence of severe infection (8%) during the relatively brief period of treatment. Of 24 patients in whom infection was diagnosed, 17 had no evidence of myelosuppression. The causative organisms included viruses, fungi, and bacteria of both high and low pathogenicity. Two-thirds of the infections were fatal. It is suggested that dCF may cause a syndrome similar to severe combined immunodeficiency during the course of treatment. Patients treated with dCF who show evidence of infection, even in the absence of neutropenia, should receive vigorous and rapid diagnostic evaluation to establish the cause of their infection, and aggressive treatment of suspected organisms. [Cancer Treat Rep 70:1117-1120, 1986]

A tight-binding inhibitor of adenosine deaminase (ADA), pentostatin (dCF), was introduced into clinical trials in 1979. Devoid of antitumor activity in the preclinical screens (1), dCF was developed by the National Cancer Institute (NCI), Bethesda, MD, for clinical use in combination with purine antimetabolites (eg, vidarabine) to prevent their rapid inactivation and thereby to permit exploration of their antitumor activity (2). Preclinical in vitro studies (3) and analogy with severe combined immunodeficiency (SCID), a disorder caused by genetic absence of ADA activity (4), predicted lymphopenia as a major toxic effect of dCF. They did not predict the significant and durable responses induced by dCF in lymphoid neoplasms, as observed in the initial phase I trials (5–7). This unexpected antineoplastic activity was accompanied by toxicity that was often severe and unpredictable, especially to the kidneys, central nervous system, and liver (5–7). It may be noted that toxic effects to these organs are not a common feature of SCID, an observation of interest in defining the precise biochemical perturbations consequent on ADA inhibition (8). SCID is, however, characterized by frequent, severe, and often unusual infections. By evaluating the cases treated to date with dCF in NCI-sponsored trials, this study sought to identify and characterize the infectious complications associated with its use.

PATIENTS AND METHODS

The 300 patients entered in phase I and early phase II trials of dCF were the subjects of this analysis. Detailed toxicity reports were submitted to the Investigational Drug Branch, NCI. Twenty-four patients were diagnosed with severe infections during, or shortly after, dCF treatment. This report compiles and analyzes these patients who have previously been discussed in abstract form (9–11).

The patients' pretreatment characteristics are shown in table 1. The spectrum of disease types, predominantly

TABLE 1.—Pretreatment patient characteristics

Characteristic	No. of patients
Severe infection	24
Median age in yrs (range): 43 (9–66)	
Sex	
Male	20
Female	4
Disease	
Acute lymphocytic leukemia	4
Diffuse poorly differentiated lymphocytic lymphoma	4
Nodular poorly differentiated lymphocytic lymphoma	2
Chronic lymphocytic leukemia	2
T-cell chronic lymphocytic leukemia	4
Mycosis fungoides	3
Hodgkin's disease	2
Myeloma	2
Mesothelioma	1
Median total dose of dCF in previous course, mg/m^2 (range): 25 (8–160)	

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[2] Presented in part at the American Society of Hematology, San Francisco, CA, Dec 1983.

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lymphoid, is uncharacteristic of early trials, but reflects the responsiveness of such neoplasms noted at an early stage (5). A wide range of dCF doses had been administered before the onset of infection, but the median dose is within the therapeutic range for most of these disorders. All patients had received prior chemotherapy.

RESULTS

The infectious episodes described in these 24 patients are shown in table 2. Only one patient had myelosuppression in the absence of marrow involvement with tumor. This 19-year-old male with diffuse poorly differ-

TABLE 2.—Infectious episodes among patients on dCF trials

Patient No.	Age/sex	Disease*	Total dCF dose administered (mg/m^2)	Myelosuppression	Other toxicity	Site	Organism	Outcome
1	19/M	DPDL	10/d × 5	+	—	Pneumonia	?	Death
2	55/M	MF	4/d × 2	Inevaluable	CNS	Pneumonia	?	Death
3	9/M	ALL	10/d × 5	Inevaluable	—	Pneumonia	?	Recovered
4	18/M	T-ALL	15/d × 3	Inevaluable	—	Pneumonia	*Candida albicans*	Death
5	26/M	ALL	20/d × 2	Inevaluable	CNS	Pericarditis	*Candida albicans*	Death
6	27/M	ALL	40/d × 4	Inevaluable	CNS	Pneumonia	Herpesvirus	Death
7	52/M	T-CLL	5/d × 6	Inevaluable	—	Blood	*Staphylococcus aureus*	Death
8	18/M	Hodgkin's disease	5/d × 5	—	—	CNS	*Listeria monocytogenes*	Recovered
9	41/M	DPDL	2-4/d × 5	—	—	CNS	*Aspergillus flavus*	Death
10	55/M	Sézary syndrome	5/d × 2	—	—	Pneumonia	*S. epidermidis*	Death
11	43/M	NPDL	5/d × 2†	—	—	Pneumonia, zoster	Varicella	Death
12	11/M	DPDL	10	—	Renal	Pneumonia	?	Death
13	59/M	Mesothelioma	10/d × 5	—	Renal, hepatic	Pneumonia	?	Death
14	32/M	Hodgkin's disease	7.5/d × 3	—	Renal	Pneumonia	?	Death
15	61/M	CLL	4/d × 3	—	Renal	Pneumonia	?	Death
16	51/M	Myeloma	5/d × 6	—	—	Pneumonia	?	Recovered
17	66/F	MF	5/d × 3	—	Renal	Septic shock	Gram-negative bacillus	Recovered
18	47/M	T-CLL	5/d × 6†	—	—	Blood	*Haemophilus influenzae*	Death
19	64/M	T-CLL	5/d × 3†	—	—	Blood	*S. aureus* with *Streptococcus hemolyticus*	Death
						Skin	Herpesvirus	
20	65/F	NPDL	5/d × 5	—	—	Blood?	?‡	Recovered
21	43/M	T-CLL	4/d × 4	—	—	Septic shock	?	Death
22	54/M	DPDL	5/d × 5	—	—	Disseminated herpes zoster	Varicella	Recovered
23	37/F	MF	5/d × 3†	—	Keratitis	Disseminated herpes zoster	Varicella	Recovered
24	45/F	Myeloma	5/d × 5†	—	—	Disseminated herpes zoster	Varicella	Recovered

*DPDL = diffuse poorly differentiated lymphocytic lymphoma; MF = mycosis fungoides; ALL = acute lymphocytic leukemia; T-ALL = T-cell acute lymphocytic leukemia; T-CLL = T-cell chronic lymphocytic leukemia; NPDL = nodular poorly differentiated lymphocytic lymphoma; and CLL = chronic lymphocytic leukemia.

†Multiple previous courses of dCF.

‡Organism never recovered but rapid response to antibiotics.

entiated lymphocytic lymphoma developed a pneumonia of undetermined etiology. Six patients, four of whom had acute lymphocytic leukemia, were inevaluable for myelosuppression because marrow involvement with tumor had produced pancytopenia before dCF was begun. Three of these patients had evidence of dCF-induced neurotoxicity. One patient developed candidal pericarditis; one, candida pneumonia; one, herpetic pneumonia; two, pneumonia of undetermined etiology; and one, *Staphylococcus aureus* septicemia. The infections were fatal in five of the six patients.

The remaining 17 patients had no evidence of myelosuppression and in particular were not neutropenic. Associated toxic effects consisted of renal impairment in five patients and keratitis in one. The infections, which were fatal in ten of the 17 patients, were varied in site and etiology. Two patients developed meningitis, caused by *Aspergillus* in one and *Listeria monocytogenes* in the other. Seven patients had clinical and radiologic features of pneumonia, the etiology of which was *Staphylococcus epidermidis* in one, varicella (associated with disseminated herpes zoster) in one, and undetermined in five. Bacteremia, in the absence of a septic focus, was documented in three patients: the causative organisms were a gram-negative bacillus (one patient), *Haemophilus influenzae* (one), and *Staphylococcus aureus* with *Streptococcus hemolyticus* (one). The last patient had associated skin lesions colonized with herpesvirus. One patient developed fever and clinical signs of sepsis; she improved rapidly with broad-spectrum antibiotics. Another patient, whose blood cultures also failed to yield an organism, died with fever and rapidly progressive septic shock. Three patients with disseminated zoster without pneumonia all recovered.

Immunologic testing was not performed on these patients, nor are biochemical data concerning the degree of ADA inhibition or deoxyadenosine levels available.

DISCUSSION

This study reveals a disturbing incidence of severe, and often fatal, infection in association with dCF therapy in early phase I trials. The nature and severity of the infections, caused by organisms of both high and low pathogenicity, suggest an immunosuppressive effect of dCF and produce a clinical syndrome which mimics SCID. Immunosuppression was recognized in early preclinical studies as a potential toxic effect of dCF (12), and its occurrence has been documented in a patient who received several courses of dCF (13). Recent studies in the mouse associate the impairment of immune function with the selective toxicity of dCF to T-cell subpopulations (14).

The basis for the infectious diathesis may exist at several levels. The increased deoxyadenosine levels which follow dCF administration are toxic to lymphocytes, both resting (15) and dividing (16). T cells are more sensitive than B cells (17), which may relate to the higher ADA activity seen in the former. It may be noted from table 2 that the doses of dCF were generally much higher than those which have been shown to cause accumulation of deoxyadenosine and its higher phosphates in the cells of most patients (6,7). Therefore, the ablation of ADA activity (at least for a time) is likely to have been achieved in all of the patients.

With complete inhibition of ADA, dCF has been shown to impair macrophage (18), monocyte (19), and NK cell (20) function in a small number of in vitro studies. Mice treated with dCF demonstrate enhanced graft acceptance (21,22) and impaired delayed hypersensitivity (22). Thus, a number of important immunologic defenses are impaired by dCF.

On the other hand, it is well-recognized that patients with chronic lymphocytic leukemia or malignant lymphoma are especially susceptible to infection. In longitudinal follow-up of such patients, infection rates of up to 50% have been described (23,24). It must, however, be emphasized that this 50% incidence is derived from a prolonged period of observation. The 8% severe infection rate in our patients arose during the brief period in which they were receiving dCF; thus, it is likely that the infections observed were due to treatment rather than to the underlying diseases.

This study confirms the suspicion that the toxicity of dCF to cells of the immune system might have important clinical consequences. Future trials with dCF should attempt to further characterize the nature of the immunologic lesion produced. Clinical studies should document the incidence of unusual infections, and patients in whom infection is suspected during dCF treatment should be rapidly and vigorously evaluated diagnostically. Suspected organisms should be treated aggressively. Awareness of this toxic effect of dCF will increase the safety of its administration and thereby enhance its therapeutic index.

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Treatment of Kaposi's Sarcoma in Acquired Immunodeficiency Syndrome With an Alternating Vincristine-Vinblastine Regimen[1]

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Twenty-four patients with acquired immunodeficiency syndrome and Kaposi's sarcoma (KS) were treated with a regimen alternating vincristine with vinblastine on a weekly basis. Objective responses to this regimen were observed in nine patients (45%), and seven (35%) had stabilization of progressive KS. Few toxic effects were observed. Alternating vincristine-vinblastine therapy is well-tolerated and effective palliative treatment for KS in acquired immunodeficiency syndrome. [Cancer Treat Rep 70:1121-1122, 1986]

Kaposi's sarcoma (KS) associated with the acquired immunodeficiency syndrome (AIDS) is often a widespread and aggressive malignancy. While both vinblastine and vincristine have each demonstrated single-agent activity in this disease (1,2), vinblastine often results in myelosuppression necessitating dose reduction (1); vincristine-induced peripheral neuropathy is a frequent cause of subjective toxicity.[3] In an effort to reduce these treatment-associated toxic effects while administering full doses of each drug, we have designed a regimen which alternates vincristine and vinblastine on a weekly basis.

PATIENTS AND METHODS

Twenty-four homosexual men with AIDS-related KS were entered in the study between July 1984 and April 1985. The median age was 35 years (range, 25-52), and the median Karnofsky performance status was 90% (range, 70%-100%). All patients had biopsy-proven KS. The median number of cutaneous lesions at the start of therapy was 33 (range, seven to 239 lesions). All patients had progressive disease at the time of initiation of therapy as evidenced by the regular appearance of new cutaneous lesions. Patients were not evaluated for the presence of visceral disease. Two patients had previous opportunistic infection and five had fever, night sweats, or weight loss. Seventeen patients had received no prior therapy, three had received prior therapy with Interleukin-2, two had received therapy with razoxane, one had received therapy with vincristine, and one had had radiation therapy.

Vincristine (2 mg) was administered by rapid iv infusion on odd-numbered weeks. Vinblastine (0.1 mg/kg) was administered by rapid iv infusion on even-numbered weeks. The vinblastine dose was reduced for wbc counts $< 3000/mm^3$ or platelet counts $< 50,000/mm^3$. Vincristine was discontinued for detectable-to-moderate muscle weakness or severe paresthesias. The dose was reduced for moderate paresthesias. In general, patients with decreased deep tendon reflexes and mild paresthesias continued to receive full doses of both drugs.

Patients were evaluated for response every 4 weeks. Complete response was defined as no evidence of residual tumor; partial response was defined as a $\geq 50\%$ decrease in the number of lesions or in the sum of the perpendicular diameters of five index lesions; stable disease was defined as a $< 50\%$ decrease in residual tumor in the absence of disease progression; and progressive disease was defined as a $\geq 25\%$ increase in residual tumor.

RESULTS

Response and Survival

Of the 24 patients, three were considered inevaluable for response: two patients developed *Pneumocystis carinii* pneumonitis during the first month of treatment, and one was lost to follow-up prior to initial evaluation at 4 weeks. Of the 21 evaluable patients, one (5%) achieved complete response; eight (38%) achieved partial response; seven (33%) had stable disease; and five (24%) had disease progression. The median time to response was 13 weeks, and the median duration of response has not been reached at 35 weeks. Eight patients continue to respond at 52, 48, 44, 41, 41, 36, 36, and 34 weeks. Three of these eight patients have had treatment

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discontinued: one following documentation of complete response; one due to severe neurotoxicity; and one discontinued treatment on his own despite absence of toxicity. Median survival has not yet been reached at 38 weeks. *Pneumocystis carinii* pneumonitis developed in four patients, toxoplasma encephalitis in one, and cytomegalovirus retinitis in one. There have been six deaths. All four patients who developed *Pneumocystis carinii* pneumonia have died. In addition, one patient died from unknown cause and one from toxoplasmosis, for which treatment was being administered prior to the start of protocol therapy.

Toxicity

The most significant toxicity observed was peripheral neuropathy. Severe muscle weakness and paresthesias were not observed, but three patients (12%) who developed detectable-to-moderate muscle weakness had therapy discontinued. Six patients (25%) developed mild paresthesias not requiring dose reduction. Four had mild constipation. One patient had severe malaise and two had mild nausea. Hematologic toxicity was minimal. Mean wbc count nadir was $3.6/mm^3$ (range, 2.0–6.3) compared with a pretreatment value of $5.1/mm^3$ (range, 2.7–7.6). Two patients each had two episodes of severe neutropenia (polymorphonuclear neutrophil count $< 500/mm^3$). None of these episodes were complicated by fever. The mean platelet count rose from 209,000/mm^3 (range, 75,000–348,000) prior to treatment to 224,000/mm^3 (range, 121,000–374,000) during treatment, and the mean hemoglobin nadir was 12.4 g/dl (range, 8.9–15.8) compared to a pretreatment value of 12.5 g/dl (range, 9.1–17.7).

Overall, 86% of the planned total vinblastine doses and 90% of the planned vincristine doses were administered.

DISCUSSION

The morbidity associated with more advanced KS, which may cause pain, lymphatic obstruction, disfigurement, and respiratory compromise, demands that palliative treatments with little associated toxicity be developed and utilized early in the course of disease in an effort to delay such complications and for cosmetic reasons. Vincristine and vinblastine are active single agents in AIDS-related KS (1,2) and have frequently been employed due to their relatively low incidence of associated toxicity and because they are less likely to cause further immune compromise. However, vinblastine administration frequently results in neutropenia, and our early experience suggested a very high incidence of moderate-to-severe neurotoxicity associated with weekly vincristine administration.[3]

The present regimen, utilizing both drugs on an alternating weekly basis, is associated with minimal myelosuppression, and the low incidence of neurotoxicity represents a significant improvement over earlier experience with vincristine alone (2).[3]

The objective response rates observed are comparable to those observed in prior studies utilizing each drug individually and suggest that this is an effective treatment regimen. Differences in response rates between various studies probably reflect the difficulty of response assessment in this disease, the use of different response criteria, and the heterogeneous and unpredictable nature of the disease itself. The use of total lesion counts in response assessment, while unconventional with respect to other malignancies, has become an accepted method for response assessment in this new disease (1,4). For many patients, measurement of cross-sectional areas of indicator lesions is inaccurate, since measurements of these lesions may remain stable while the patient continues to develop multiple new cutaneous lesions, often at a rapid rate. Conversely, the extraordinarily large number of lesions that some patients develop make lesion counts in these patients both impractical and inaccurate. Some degree of subjectivity is necessarily involved in deciding which is the most appropriate measure of response in a given patient.

In the absence of a randomized trial, it cannot be stated that the use of this treatment regimen results in improved response rates in comparison to the single agents used alone. However, we feel that alternating vincristine-vinblastine is a very well-tolerated and effective palliative chemotherapeutic regimen for patients with AIDS-related KS. This regimen continues to be highly successful in our clinic and has become our standard chemotherapy regimen for patients with AIDS-associated KS.

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Phase II Study of Fludarabine Phosphate for the Treatment of Advanced Non-Small Cell Carcinoma of the Lung: A Southwest Oncology Group Study[1,2]

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Fludarabine phosphate (2-FLAMP), an analog of vidarabine with preclinical antitumor activity in the LX-1 human lung cancer xenograft and clinical evidence of activity against lung cancer in phase I trials, was evaluated in a phase II study of patients with non-small cell lung cancer (1–3).

Patient eligibility criteria for this study required the following: histologically proven recurrent or metastatic non-small cell cancer of the lung; performance status (Southwest Oncology Group criteria) of 2 or better and life expectancy of 6 weeks; no prior chemotherapy; measurable or evaluable disease; bone marrow and renal function consistent with adequate tolerance to treatment with 2-FLAMP; and written informed consent for the treated patients. 2-FLAMP was administered iv over 30 minutes at a dose of 18 mg/m^2 daily for 5 days, repeated every 28 days. Dose escalation to 22 mg/m^2/day was permitted. Standard response criteria were used.

Of 23 patients entered in this study, 19 were fully evaluable for both response and toxic effects. Three patients had early deaths and were inevaluable for toxic effects. One patient had received prior irradiation to a measurable lung lesion without pretreatment evidence of disease progression; this patient was ineligible, but was considered evaluable for toxic effects. Patient characteristics and toxic effects are shown in table 1.

TABLE 1.—Patient characteristics*

Characteristic	
Entered	23
Eligible (males/females)	22 (14/8)
Evaluable for toxic effects	20
Median age in yrs (range)	60 (43–77)
Median performance status (range)	2 (0–2)
Histology	
Squamous cell carcinoma	5
Large cell carcinoma	5
Adenocarcinoma	9
Mixed cell carcinoma	1
Alveolar carcinoma	1
Other non-small cell carcinoma	1
Courses evaluable for toxic effects	
18 mg/m^2/day × 5	25
22 mg/m^2/day × 5	10
Toxic effects (No. of courses)	
Nausea and vomiting	11
Oral mucositis	1
Leukopenia†	19
Thrombocytopenia	2
Anemia‡	5
Neurotoxic effects	11
Rash	1

*Unless otherwise specified, values = No. of patients.
†Median wbc count (range): 3100 cells/mm^3 (1500–3900).
‡Median Hgb count (range): 10.1 g/dl (7.5–10.9).

Neurotoxic effects included transient mild-moderate somnolence or fatigue, transient paresthesias, and twitching of the extremities. One patient experienced the acute onset of dementia 41 days after beginning a second course of 2-FLAMP at a dose of 22 mg/m^2/day × 5. Evaluation included a computerized tomographic scan of the brain which revealed mild cerebral atrophy and cerebrospinal fluid analysis which showed a protein of 140 mg/dl. Progressive mental obtundation ended in the patient's death 9 days after the onset of the mental status abnormalities. Autopsy was refused by the patient's family. Although severe central nervous system toxic effects induced by 2-FLAMP therapy were suspected, other causes such as carcinomatous meningitis could not be ruled out.

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Twenty-two patients were evaluable for response to therapy. No antitumor responses were observed (95% confidence interval, 0%–15%).

Other studies of 2-FLAMP at high dose for the treatment of leukemia and at doses similar to those used in this study have been accompanied by the sporadic occurrence of severe neurologic symptoms and signs including blindness, encephalopathy, seizures, and paresis (4). Until the frequency and nature of the neurologic sequelae of 2-FLAMP administration are better understood, and based on the response data generated in this study, further evaluation of 2-FLAMP in the treatment of non-small cell lung cancer cannot be recommended.

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Phase II Trial of Mitoxantrone in Advanced Primary Liver Cancer: A Cancer and Leukemia Group B Study[1,2]

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Mitoxantrone is a DNA intercalator which animal studies have shown is as active against tumors as doxorubicin with considerably less cardiotoxicity (1). Clinical studies demonstrate promising results in acute leukemias, lymphomas, myeloma, and advanced breast cancer, whereas outcomes have been less encouraging in other malignancies (1,2). In 1981, the Cancer and Leukemia Group B (CALGB) began a phase II trial of mitoxantrone for primary liver cancer, a disease in which doxorubicin has some activity.

Patients with measurable, histologically confirmed, unresectable, or metastatic primary liver cancer (hepatocellular carcinoma, cholangiocarcinoma, or mixed carcinoma) were eligible provided they had: given informed consent; wbc count $\geq 4000/\mu l$; platelet count $\geq 100{,}000/\mu l$; hemoglobin ≥ 10 g/dl; BUN ≤ 25 mg/dl; creatinine ≤ 1.5 mg/dl; bilirubin ≤ 5.0 mg/dl; no other malignancies; cumulative dose of doxorubicin < 400 mg/m^2; and no prior exposure to mitoxantrone, Mitoxantrone diluted in normal saline or 5% dextrose was administered iv over at least 10 minutes every 3 weeks. The dose was 12 mg/m^2 for patients with adequate hepatic function and 9 or 6 mg/m^2 for patients with significantly elevated SGOT or bilirubin. Subsequent reductions for toxic effects were permitted.

Thirty-eight patients were entered in the study. Two patients never began treatment and three were ineligible based on histologic review. Table 1 shows characteristics of the remaining patients. All data were reviewed by the protocol chairman. Standard CALGB toxicity and solid tumor response criteria (3) were used.

One complete response of 9 weeks' duration and one partial response of 9 months' duration were observed (response rate, 6%). These responses occurred in the patients with the lowest initial bilirubin levels, both

TABLE 1.—Patient characteristics and results

Characteristic	% of patients
Total No. of patients: 33	
Median age in yrs (range): 62 (15–77)	
No. of males/females: 22/11	
CALGB performance status	
0	22
1	44
2	31
3	3
Histology	
Cholangiocarcinoma	6
Hepatocellular carcinoma	82
Mixed carcinoma	3
Not reported	9
Prior treatment	
Surgery	12
Chemotherapy (including anthracyclines)	21 (18)
Initial bilirubin (mg/dl)	
< 0.5	27
0.5–0.9	30
1.0–1.9	24
2.0–3.5	12
> 3.5	6
Response	
Complete	3
Partial	3
Disease improvement	3
Stable disease	12
Disease progression	76
Unevaluable (early death)	3
Toxic effects graded severe or worse	
Hemoglobin (< 8 g/dl)	3
Wbc count (< 2000/dl)	22
Platelet count (< 75,000/dl)	12
Cardiac (described in text)	3
Diarrhea (> 5 watery stools/day)	3

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having hepatocellular histology. Median survival for all patients was 21 weeks, with 23% survival at 1 year (24 weeks and 29% for hepatocellular histology). The toxic effects reported were primarily hematologic. One patient was removed from the study following a sharp drop in ejection fraction (no other cardiac symptoms).

These data show limited activity of mitoxantrone in liver cancer, consistent with preliminary results of a similar study conducted by the Eastern Cooperative Oncology Group (4).

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Phase II Clinical Trial of Diaziquone in the Treatment of Patients With Recurrent Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study[1,2]

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Diaziquone (AZQ) is a rationally synthesized quinone derivative exhibiting antitumor activity in several rodent tumor models (1) and several human tumor xenografts. Phase II human trials were initiated by the Gynecologic Oncology Group (GOG) in December 1981 to evaluate the activity of AZQ in gynecologic cancer. One complete response and one partial response were noted among 25 patients with recurrent epithelial ovarian cancer (2).

MATERIAL AND METHODS

Thirty-one patients with squamous cell carcinoma of the cervix refractory to standard antitumor therapy were entered in the study. A BUN $\leq$ 25 mg/100 ml, serum bilirubin $\leq$ 1.0 mg/100 ml, serum creatinine $\leq$ 2.0 mg/100 ml, and SGOT $\leq$ 50 IU/L were required. Pretreatment wbc and platelet counts $>$ 4000/mm^3 and 150,000/mm^3, respectively, were required for entry. Patient characteristics and treatment results are shown in table 1. Three patients were ineligible (incorrect histology); two others were inevaluable (never received protocol therapy). Twenty-six patients were evaluable.

AZQ was administered iv over 20 minutes at a dose of 22.5 mg/m^2 diluted in 150 ml of normal saline. For subsequent courses of treatment, the dose was escalated to 30 mg/m^2 if the granulocyte and platelet count nadirs did not fall to $<$ 1500/mm^3 and 100,000/mm^3, respectively.

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Entered	31
Evaluable	26
Median age in yrs (range): 49 (35–71)	
Performance status*	
0	4
1	13
2	9
Prior therapy	
Surgery	10
Radiation therapy	25
Chemotherapy	26
Site of recurrent disease	
Pelvis	14
Outside pelvis	12
Tumor grade	
1	1
2	17
3	8

*Gynecology Oncology Group criteria.

An adequate trial was defined as receiving one course of treatment and surviving at least 3 weeks. All patients remained in the study until there was evidence of disease progression. Response, performance status, and tox-

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[2] Supported by Public Health Service grants (CA) from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. The following institutions participated in this study: George Washington University Medical Center, Washington, DC (CA-16938); University of Oregon Health Sciences Center, Portland; Duke University Medical Center, Durham, NC (CA-12534); University of Minnesota Medical School, Minneapolis (CA-23088); University of Mississippi Medical Center, Jackson (CA-13633); The Milton S. Hershey School of Medicine of Pennsylvania State University, Hershey (CA-16386); Georgetown University Hospital, Washington, DC (CA-16938); University of North Carolina School of Medicine, Chapel Hill (CA-23073); University of Texas Health Science Center at Dallas (CA-28160); Indiana University Medical Center, Indianapolis (CA-21720); Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, NC (CA-21946); The Albany Medical College of Union University, NY; University of California Medical Center at Irvine (CA-23765); Illinois Cancer Council, Chicago (CA-27806); St. Louis University Medical Center, MO (CA-35571); and Jacksonville University Hospital, FL. J. A. Blessing is a Cancer Research Scientist V.
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icity grades were defined according to previously described GOG criteria (3).

RESULTS

One partial response was noted; a 67-year-old woman with a pelvic mass (14 × 10 cm) measured by physical examination had a reduction to 7 × 6 cm after two courses of AZQ, received a total of four courses of AZQ, and had disease progression 2 months later. Of the remaining 25 patients, nine had stable disease, while 16 had progressive disease.

The median number of courses administered was two (range, one to 13). All patients were evaluable for toxic effects. A leukocyte count $< 3000/mm^3$ was seen in nine patients and was life-threatening ($< 1000/mm^3$) in one. A platelet count $< 100,000/mm^3$ was seen in six patients and was life-threatening ($< 25,000/mm^3$) in two; 16 patients had no leukopenia or thrombocytopenia. Subsequent doses were escalated to 30 mg/m^2 in seven patients. Escalation was not accomplished in nine patients due to grade 2 or greater toxic effects. Cumulative toxic effects were not observed. Six patients had nausea and vomiting which were controlled with antiemetics. Eighteen patients had no gastrointestinal side effects. Thirteen patients had anemia with hemoglobin levels < 9.5 g/dl. Anaphylaxis was not seen in any of the patients. Median time to disease progression was 1.5 months and median survival was 5 months.

CONCLUSION

Based on the activity observed in this group of patients there does not appear to be a significant role for AZQ at the dose and schedule tested as a salvage agent in advanced squamous cell carcinoma of the cervix.

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Phase II Study of Spirogermanium in Metastatic Prostate Cancer[1]

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Spirogermanium is an azaspirane-germanium compound that was discovered by Rice et al in 1974 (1). It has cytotoxic activity against HeLa cells, human lymphoma cells, Walker 256 carcinosarcoma, 13762 mammary adenocarcinoma, and 11095 prostatic carcinoma (2). In men, the dose-limiting toxic effect is neurological. Legha et al (3) showed that higher doses could be administered by continuous infusion than were possible by short iv schedules. Therefore, we initiated a study of the continuous infusion of this drug in patients with metastatic prostate cancer.

MATERIALS AND METHODS

Fifteen patients with metastatic prostate cancer resistant to hormonal therapy and who were previously untreated with chemotherapy were entered in the study. Spirogermanium was administered by continuous iv infusion through a centrally placed iv line with portable infusion pumps at a dose of 150 mg/m^2/day for 28 days. These courses were repeated every other month. Spirogermanium was supplied by the Division of Cancer Treatment, National Cancer Institute, Bethesda, MD.

For measurable disease a partial response was defined as a $>$ 50% decrease in the size of all measurable lesions. Osseous metastasis required all of the following: improvement in bone pain; improvement in bone scan; and a 50% decrease in the elevation of alkaline and prostatic acid phosphatase levels on three separate occasions.

TABLE 1.—Patient characteristics and toxic effects

Characteristic	No. of patients
Total	15
Median age in yrs (range): 66 (52–70)	
Zubrod performance status	
Level 1	9
Level 2	5
Level 3	1
Site of disease	
Bone	12
Bone and liver	2
Bone and skin	1
Evaluable patients	15
Toxicity and response	13
Toxicity only	2
Neurologic toxic effects	
Blurred vision	9
Vertigo	6
Confusion	5
Hand tremor	5
Sensory neuropathy	3
Electroencephalogram abnormality	2
Headache	1
Cogwheel rigidity	1
Hearing loss	1
Other toxic effects	
Hepatic transaminase elevation (2–5 × normal)	4
Skin toxicity (hyperkeratosis)	1

RESULTS

Patient characteristics and toxic effects are shown in table 1. Spirogermanium at 150 mg/m^2/day by continuous infusion was given for a median number of 27 days (range, 4–71). Two patients were evaluable only for toxic effects because they developed severe neurotoxic effects after 4 and 6 days of treatment. Of the remaining 13 patients who were evaluable for response, 11 developed progressive disease and two had no change after 28 and 71 days of treatment, respectively. These latter patients also developed severe neurotoxic effects, which required discontinuation of the drug for both. Neurotoxic effects were manifested primarily as a diffuse toxic encephalopathy. No myelosuppression was noted.

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DISCUSSION

By using continuous iv infusion of spirogermanium, we were able to deliver higher doses than were possible in other studies using short, intermittent iv schedules of administration (4,5). Despite this fact, there were no responses in 13 evaluable patients (response rate, $< 20\%$ with 90% confidence), and although they were reversible, severe and unpredictable neurotoxic effects developed in six patients. We conclude that this drug produces significant neurotoxic effects and has no significant activity at the dose and schedule used in patients with metastatic prostate cancer.

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"Some Thoughts on the Future of Clinical Trials in Cancer"

The Editorial "Some Thoughts on the Future of Clinical Trials in Cancer" by Wittes et al (1) contained much food for thought. This reply is intended to provide some "corporate memory" concerning the cooperative clinical trials scientific review and the Cancer Therapy Evaluation Program (CTEP), and to point out a few incorrect assertions in the Editorial.

The reason that I raise the issue of corporate memory is because the staff of CTEP has essentially turned over since 1979, when the cooperative clinical trials program of the Division of Cancer Treatment (DCT) of the National Cancer Institute (NCI) last underwent a formal external scientific review. I served on the Board of Scientific Counselors (BSC) of DCT at the time, and chaired the Board's clinical trials subcommittee. I am quite familiar with the public testimony at the BSC meetings which served as the background for the report that we developed for the Board in 1980. The Editorial stated that the previous review "made no attempt to evaluate the methodology used in the conduct, analysis, and reporting of trials." Further, it added "Nor did it really attempt to evaluate critically the quality of ideas submitted to clinical testing or the timeliness of their implementation." I would hold that this is incorrect, as the quality of the trials, the source of new ideas, and the effectiveness of their study were, in fact, major issues discussed by the BSC, by its invited consultants, and particularly at the subcommittee meetings (which were attended by CTEP staff).

As one example, during the public testimony, Dr. Marvin Zelen quantified the importance of seminal pilot studies in serving as the basis for positive randomized clinical trials, and demonstrated persuasively that large-scale randomized trials established without a positive pilot study have a greater chance of being negative. Dr. Zelen's presentation provided persuasive evidence to the subcommittee of the importance of setting up a formal mechanism for pilot studies within the groups to better perfect treatments and identify those which warranted being subjected to prospective randomized trial. As a result, a formal pilot study program has been established in the groups and is providing leads for large clinical trials.

The BSC dealt with methodology directly by recommending a new granting mechanism to the NCI for cooperative group activities, "the Cooperative Agreement," which is used by the Government in areas wherein "substantial involvement of government" is desired in a given activity. The purpose of this was not only to minimize duplication, but to enhance interchange of ideas between CTEP and the various groups, to facilitate intergroup studies for larger-scale trials, and to increase the likelihood that important new ideas would be brought into controlled clinical trials with assured excellence in study design. Furthermore, the CTEP staff was enlarged to increase its capability to carry out this important mission. Since the time of implementation of the subcommittee recommendations, CTEP has clearly shared equally in the responsibility for developing major randomized trials approved for group study, and has had the opportunity to enhance communications between the groups and their disease committees and to aid in the introduction of new ideas. Thus, any aspersions to be cast upon the groups must be shared by CTEP, which was given the funding mechanism, the staff, and the responsibility to be substantially involved in this effort. This critical role of CTEP is not clearly described in the Editorial. The Editorial criticizes the groups, and in some instances, unfairly.

The Editorial includes a listing of scientific questions considered to be very important by its authors, and implies that they have not been adequately addressed by the groups [eg, somatic mutation theory (Goldie-Coldman Hypothesis), perioperative therapy, high-dose drug administration, regional chemotherapy, and the use of interferon in indolent lymphomas]. I suspect that many clinical investigators would disagree with the perspectives of the Editorial. For purposes of brevity, I will cite one example which I consider to be most egregiously cast off by the authors as "a major failing" in the theoretical or practical planning of clinical trials by the cooperative groups. This specific example relates to the testing of the Goldie-Coldman hypothesis. I am most familiar with the activities in the group in which I participate [the Southwest Oncology Group (SWOG)]. I believe that this hypothesis has, in fact, been placed to the test in a number of tumor types in pilot studies and in several major tumor types in large-scale randomized trials by SWOG. This is despite the agreed-upon difficulty of defining appropriate regimens of at least partially non-cross-resistant chemotherapy (which of course requires suitable pilot data). I have served as chairman of the SWOG myeloma committee over the past decade, and have overseen an effort to systematically develop non-cross-resistant regimens. Subsequent to the formulation of the Goldie-Coldman hypothesis, we set out to formally test this hypothesis. Our efforts have been discussed in the group's regular minutes, in periodic study section reviews, and in our publications, and have been continuously available to CTEP. These are summarized below.

In the early 1970s, SWOG developed a series of drug

combinations for the treatment of myeloma which each had approximately equivalent efficacy and toxicity [VMCP (vincristine, melphalan, cyclophosphamide, and prednisone); VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisone); and VBAP (vincristine, carmustine, doxorubicin, and prednisone)] as established in SWOG study 7418 (2). We also established that the VBAP combination was at least partially non-cross-resistant with conventional alkylating agents such as melphalan or cyclophosphamide, and the VMCP combination (3). In SWOG study 7704/7705, which I coordinated, we first tested the syncopated alternation of VMCP/VBAP, giving three cycles of VMCP followed by three cycles of VBAP, etc, and directly compared these alternating combinations to MP (melphalan/prednisone). The results of that study showed clear superiority of the alternating combinations, with a marked improvement in survival as compared to MP or prior combination studies (4). Subsequently, in protocol 7927/7928, the VMCP/VBAP syncopation was compared to VCP (vincristine, cyclophosphamide, and prednisone), and again marked superiority of alternating combinations was observed (5). Furthermore, in the course of analysis of this latter study, the 7704/7705 long-term results were reanalyzed, and we found a significant number of 8-year survivors from the former study (5). These results culminated in our developing the current protocol (SWOG 8229/8230), which has as one of its principal scientific questions the direct testing of the Goldie-Coldman hypothesis. In this study, patients receive the syncopated alternation of VMCP/VBAP for remission induction, or an every-3-week alternation of the two equitoxic regimens as would be predicted to be superior in the Goldie-Coldman hypothesis. Over 450 patients have already been randomized for the remission induction program, and the study has been maturing quite well; case accrual will soon be completed. The myeloma experience to date has been quite encouraging, and we look forward with interest to the further maturation of the current trial and the prior trials of alternating combination chemotherapy carried out by SWOG over the past 9 years. As an additional example, in SWOG protocol 8012 for large cell and adenocarcinoma of the lung, chemotherapy with alternating regimens has been compared to the use of either of the two regimens alone in 452 patients. This latter study has recently reported a modest but significant improvement in survival of patients with non-small cell lung cancer treated with the alternating combination chemotherapy (6). I point out these examples to indicate that SWOG has, in fact, committed substantial patient resources in efforts to test the somatic mutation hypothesis in several signal tumor types.

The purpose of this Letter is not to criticize the authors overall, but merely to point out that there are some inaccuracies in their analysis. The staff of CTEP has, from my perspective, made serious and constructive efforts to improve the clinical trials program. I suspect that other investigators involved in the cooperative clinical trials program might wish to debate other specific areas in the Editorial.

The Editorial, per se, is not a mandate for change, and a dialogue is clearly needed. This is not to imply that further change in the clinical trials program should not be considered. The appropriate forum in which to objectively examine the DCT's overall clinical trials program is before the DCT Board. This is particularly the case when the Director of CTEP also serves as the editor of *Cancer Treatment Reports.* Peer review of the individual cooperative groups is, of course, the responsibility of the Cancer Clinical Investigations Review Committee Study Section, and this process should, of course, continue. However, for evaluation of the overall clinical trials process and its scientific accomplishments and directions, I believe that a formal Board review with detailed presentations of the science by the investigators is needed. It would serve as an appropriate follow-up of the DCT Board's 1979–1980 review, and should be undertaken before any additional major changes are implemented in the overall structure of the cooperative clinical trials program.

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"Some Thoughts on the Future of Clinical Trials in Cancer"

This Letter is in response to the Editorial entitled "Some Thoughts on the Future of Clinical Trials in Cancer," which appeared in the February 1986 issue of *Cancer Treatment Reports* (1). I would like to comment on the portion of the article which deals with the current intergroup prostate protocol. While the summary of the events is accurate, it does not totally reflect the complexity of the study and the fact that it was completed in a short amount of time.

As chairman of the intergroup study and genitourinary committee chairman of the Southwest Oncology Group, I would like to review the development and enactment of the study. My first formal contact relative to the study occurred on April 25, 1984, when I received a letter from Dr. Mario Eisenberger. A meeting was held on May 16, 1984, in Bethesda, MD, to discuss the initial details and implementation of the above study. There was unanimous agreement among those present relative to the study design. It was agreed that this would be a randomized double-blind, two-arm trial comparing leuprolide plus placebo versus leuprolide plus flutamide. An executive committee was formed and a person was designated to construct the initial protocol. On July 12, the first draft of the protocol came across my desk for review. Another copy was circulated from the National Cancer Institute (NCI) on September 6, 1984. Several problems arose with the pharmaceutical companies relative to drug production, packaging, and distribution. There were also questions relative to the study design and points raised by TAP Pharmaceuticals. On October 19, 1984, a conference call was held to try to resolve the drug distribution issue and also to question the feasibility of accruing 600 patients in 2 years.

It was also decided during that conversation that a member of the executive committee needed to be designated as the intergroup chairman to orchestrate the study. Several weeks later, I assumed that position. During the next 3 weeks, members of the executive committee, in particular Dr. Peter Reese of the National Prostatic Cancer Project, raised a number of questions about the original protocol design. The protocol was rewritten, circulated, and approved within a period of 2 weeks. Unfortunately, during that time, Dr. Eisenberger left the NCI. Dr. Fred Avis began working with us. A meeting was held on January 15, 1985, at the Dallas AmFac Hotel with Dr. Fred Avis and Clarence Fortner to iron out final details of drug distribution and conduct of the study. Another meeting was held to review the data collection forms with Dr. Michael Freeman in Bethesda on February 8, 1985. Thirteen months later, 600 patients have been accrued on the protocol and it has been closed. Considering the innate complexities of this study, I consider this cooperative group effort to have been an overwhelming success.

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Testing Hypotheses in Clinical Trials: Experience of the National Cancer Institute of Canada Clinical Trials Group

The recent article by Wittes et al (1) suggests that cancer cooperative groups have failed to address certain "pressing questions" in their studies. The questions cited range from the fairly specific, such as "Interferon in the Indolent Lymphomas," to more general issues, such as testing the "somatic mutation theory" and the effects of "High-Dose Drug Administration." As we have had recent experience with studies addressing these two latter questions, we thought it might be useful to communicate some concerns about the problems inherent in trying to use clinical trials to test biologic hypotheses. The issue of testing hypotheses in clinical research has been thoughtfully addressed at a theoretical level in the book *Clinical Trials* by Schwartz et al (2). These authors distinguish between the "explanatory" and "pragmatic" aspects of clinical trials and point out that trials designed to answer pragmatic questions (ie, how to treat the next patient) are often not suited to answering explanatory questions (ie, is a specific hypothesis true) and vice versa. These concepts have been widely discussed and their importance recognized with respect to the need to include all patients randomized in a "pragmatic" or "intent to treat" analysis (3). However, the impact of decisions to pursue pragmatic or explanatory objectives on other aspects of study design and conduct seems to have been less generally appreciated. Our experience certainly supports the contention that these goals can be conflicting, and leads us to be wary of the

expectation that improvements in cooperative group organization will resolve a difficulty that is fundamental to the nature of clinical research. In the following sections, we describe several of our studies, including those referred to above, in which we attempt to address general "scientific" (ie, explanatory) as well as specific "therapeutic" (ie, pragmatic) questions. In each case, a particular difficulty in study design, conduct, or interpretation is highlighted.

Varying Convictions About Validity of a Hypothesis

One of the obvious dangers of designing clinical trials around a specific biologic hypothesis is that, however persuasive the hypothesis might be when the trial is designed, it may fall out of favor before the study is complete. There is probably no better illustration of this problem than the fate of studies conceived during the era when immunotherapy appeared to be a promising new treatment. Like many other groups, the National Cancer Institute of Canada Clinical Trials Group started several studies of immunotherapy during that period. Some of these trials failed to meet their accrual goals as this form of treatment began to be less popular. In addition, the fact that the acceptance of the underlying premise of the trials varied among individuals and over time has had a more subtle effect on the interpretation of the results of studies which were successfully completed. For example, we completed a trial of immunotherapy with "specific" tumor antigen and Freund's complete adjuvant (4) in stage I and II completely resected non-small cell lung cancer which demonstrated no overall benefit. However, the chairman of the trial noted that compliance with treatment varied among centers and that, in the centers with good compliance, the results suggested a benefit of immunotherapy. While there is no question that the appropriate "pragmatic" analysis of this trial requires inclusion of all centers (5), it is hard not to be sympathetic with the chairman's concern that his regimen was not given a fair test because it was not administered with equal fervor by all participants. The point is that the appropriate testing of a scientific hypothesis, especially one for which there is varying enthusiasm, requires a degree of discipline by physician investigators that may not occur without careful monitoring—a point to which we will return later.

A slightly different, but equally vexing, problem that can occur when convictions about a concept change is in the interpretation of a positive result when it is no longer expected. This difficulty has arisen with respect to our recently completed trial of adjuvant immunotherapy in malignant melanoma (6). Patients on the levamisole arm of this study had better survival than controls, a difference that was of borderline statistical significance. Public discussion of this result has yet to occur, but it would not be surprising if the outcome were greeted with skepticism, while 10 years ago the finding would have been accepted with equanimity. Further, a pragmatic "choose the best treatment" approach to the design of our next study would dictate that we use levamisole as the control arm, since, even if the activity of this agent has not been established beyond reasonable doubt, it is extremely unlikely, given our results, that we would cause substantial harm by treating patients in this manner. However, trials with a positive control arm of this type are unlikely to be appealing to agencies interested in "scientific" studies of new biologics. Thus, a pragmatic approach to our own results may exclude us from addressing an interesting scientific question—a position we would not be in if the conceptual framework in which we were operating had not shifted.

Disparity Between Scientific and Clinical Questions

A "pressing" question not mentioned by Wittes et al is whether "state of the art" chemotherapy prolongs survival in patients with unresectable non-small cell bronchogenic carcinoma. We have recently completed a trial addressing this question, the results of which will be available shortly. The design and conduct of this study raised some difficult methodologic questions. The one most pertinent to this discussion relates to the fact that while the scientific goal of the study was to determine if chemotherapy prolonged survival, patients receiving chemotherapy on the trial had to be managed in the absence of knowledge of the outcome. Thus, decisions on continuation of treatment had to be made on the basis of response to therapy, and patients whose disease did no better than stabilize eventually had their quite toxic treatment stopped, despite the fact that disease stabilization might represent a benefit of therapy which could conceivably translate into prolonged survival. A more purely explanatory approach might have been to require that all patients be kept on treatment until obvious disease progression or even, as in some animal experiments (7), until death. We chose, however, to take the pragmatic approach of testing the policy of giving chemotherapy as it would be administered in the real world. Again, there will probably be those who feel this means that the underlying hypothesis has not been tested with the full rigor of a scientific experiment.

Refinement of Concept During Study

One of the issues which Wittes et al feel has been inadequately addressed by cooperative groups is the role of high-dose chemotherapy. We have, in fact, been conducting a randomized trial of "high-dose" BACOP (bleomycin, doxorubicin, cyclophosphamide, vincristine, and prednisone) versus standard BACOP in poor-prognosis lymphomas since 1982. Accrual to the study has been slow but steady, and protocol compliance has been satisfactory in that patients on the higher-dose arm are receiving substantially more doxorubicin. However, concepts concerning the relationship of treatment outcome to the amount of chemotherapy given have been refined during the course of this trial. With today's knowledge we might well have designed the trial so that the effects

of total dose and dose intensity (8) could be separated. However, as it stands, the experimental arm differs from standard BACOP in both total dose and dose intensity. Thus, a positive result may be important from a pragmatic point of view, but may not answer the currently "pressing" scientific question of dose intensity in this disease.

Alternate Interpretation of Results

Wittes et al also note the failure of cooperative groups to properly incorporate the concepts derived from the "somatic mutation" theory into clinical trials. We have recently completed a study using an experimental arm which we, and others (9), feel makes maximal use of the principles of the Goldie-Coldman hypothesis. Patients with extensive small cell carcinoma were randomized between standard CAV (cyclophosphamide, doxorubicin, and vincristine) chemotherapy and alternation between CAV and etoposide/cisplatin, a regimen which appears equal in activity and non-cross-resistant to CAV (10,11). Patients on the alternating arm had significantly prolonged disease-free and overall survival (12). Despite this positive result, it is difficult to conclude that we have demonstrated the applicability of the Goldie-Coldman model to this clinical situation for two reasons. First, although the protocol required that all patients progressing on CAV receive etoposide/cisplatin, many progressed and died before an attempt at salvage could be carried out. Second, the activity of etoposide/cisplatin may be so substantial that the results on the alternating arm are simply due to the fact that more of these patients received a superior chemotherapy regimen. Thus, despite having carried out what we feel was a well designed and executed study, we still have not addressed the underlying question as unambiguously as in an animal experiment.

Conflicting Demands of Size, Simplicity, and Scientific Rigor

As Wittes et al argue and these examples illustrate, the "window of opportunity" for carrying out trials designed to address pressing scientific concepts may be narrow. Such trials need to be done in the brief interval between the time a concept is well enough developed to be worth testing and the time it has been discarded or so widely accepted that it is impossible to study. The logical solution to this problem is to carry out large studies which accrue sufficient patients quickly, and Wittes et al describe ways in which intergroup cooperation may be facilitated in order to achieve this goal. This suggestion resembles that of Yusuf et al (13), who argue that clinical trials should be very large and very simple to carry out. Certainly no one could complain about an effort to remove the complexities involved in carrying out intergroup studies. However, it is important to recognize that the large, simple studies envisioned by Yusuf et al may not satisfy the goals of those who wish to study scientific concepts. As was mentioned earlier, investigator discipline is an essential component of successful studies of controversial ideas. This discipline almost certainly requires the complicated quality control machinery now in place in modern cooperative groups. Further, the amount of data needed on, for example, the results of ancillary investigations, may be greater in studies addressing a scientific hypothesis than in those which seek only to determine which of two therapies provides better treatment for patients. Again, the goals of explanatory and pragmatic studies may conflict. An investigator who wants the answer to a therapeutic question is interested in knowing how the policy of offering a treatment will affect outcomes in the "real world." He might interpret lack of compliance with the protocol as a measure of its acceptability and, thus, consider it a component of the treatment policy. He might also be willing to dispense with all information except that pertinent to the major outcome of the trial. An investigator interested in testing scientific hypotheses would be unlikely to make these allowances and would of necessity be committed to a more complex trial design.

CONCLUSIONS

The purpose of this article is not to argue with the contention that clinical trials groups should address pressing clinical and scientific issues. We feel it is quite possible, as illustrated, for groups to do studies which deal with questions of real clinical and biologic significance. However, we do not think the difficulties involved in combining pragmatic and explanatory objectives in the same study are as widely appreciated as they should be. As we have tried to illustrate, the goals of choosing the better treatment for the next patient and testing a scientific hypothesis are not necessarily compatible. In our view, clinical trials should ordinarily be designed so that, when complete, their results at least provide a meaningful answer to a therapeutic question. If, in addition, they shed some light on a vexing biologic question, so much the better. However, to place this responsibility on all studies risks raising expectations that cannot always be fulfilled and could compromise our ability to address important, but conceptually simple, therapeutic problems.

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May 1, 1986

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"Some Thoughts on the Future of Clinical Trials in Cancer"

I read with interest the article regarding clinical trials that appeared in the February 1986 issue of *Cancer Treatment Reports* (1). In December 1983, I assumed a position in a teaching hospital in Western Massachusetts as Chief of the Hematology/Oncology Service. I set as one of my top priorities a goal of greatly increasing the accrual of patients to national protocol studies. In a community where 80% of medical oncology patients are seen by colleagues in private practice, it was obvious where our target was.

Although we have made significant improvement in clinical trials accrual, the sad fact remains that, by my best estimate, there are still > 1000 patients a year who could be candidates for trials in our area alone. This is despite the fact we have made it as painless as possible for our cooperating physicians to put patients on protocols. In addition, our collaboration with national groups would not be possible without significant subsidization of our efforts by our hospital, which pays for part of the salary of our data manager (who does nothing else but national protocol data management) in addition to part of the salaries of full-time physicians and nurses who devote much of their effort to cooperative group trial activity.

As I see protocols become more and more complex, and eligibility requirements more strict, I cannot help but sympathize with my colleagues who sometimes, after spending much time trying to establish patient eligibility, throw up their hands and put the patient on a "standard" regimen. They aren't even subsidized for their efforts, and they have absolutely no incentive for participating in group trials; in fact, it sometimes appears that cooperative groups are trying to make it even more difficult for physicians in private practice to participate.

While it is certainly reasonable to avoid duplication and, through the benign despotism of the National Cancer Institute (NCI), "direct" research along "productive" lines and set up large intergroup studies, I suspect that still another layer of bureaucracy will discourage participation in cooperative group efforts even more.

If the creation of clinical trials is to become even more distant from the practitioner who is expected to contribute patients to them, we will continue to have a shrinking pool of patients to bridge the gap between laboratory and practice; I believe it is short-sighted to pursue more efficient ways to use this shrinking pool (and thus make it shrink even more). It would be better to expand the pool in order to test new ideas more efficiently and rapidly.

The NCI should use some of its resources to study and remedy the crisis in patient acquisition to those pedestrian, but extremely important, national group clinical trials.

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June 9, 1986

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Reply: Clinical Trials

These four Letters raise many significant issues. Dr. Salmon is probably correct that our Editorial did not give adequate emphasis to the details of the clinical trials review conducted in 1980–81 under the auspices of the Board of Scientific Counselors (BSC) of the Division of Cancer Treatment (DCT). As he recounts, and as we had also emphasized, this review led to far-reaching changes in the structure of the National Cancer Institute's (NCI) clinical trials program. We do, however, stand by our original contention that the present clinical trials review provides a much more detailed evaluation of cooperative group trials in particular disease areas than previous reviews have. In these disease areas, teams of peers have evaluated study-by-study the trials performed in the group program. The result is a detailed critique of trials conduct and methodology that provides a sound basis for assessing the strengths and weaknesses of the current system. Coordination of such reviews should, we think, be a continuing activity of the Cancer Therapy Evaluation Program (CTEP) and should concentrate on the performance of the clinical trials program as a whole. This activity is not intended to supplant established peer review mechanisms for the evaluation of individual cooperative groups.

As Dr. Salmon also points out, and as we noted quite clearly in the Editorial, CTEP certainly shares with the cooperative groups responsibility for the overall effectiveness of the system. Any systematic failings—problems with coordination, excessive duplication, or suboptimal quality of the scientific questions under study—are CTEP's problems no less than those of the groups. Under the terms of the cooperative agreements supporting the group program, NCI staff has broad responsibility for these areas. As anyone with even a vestigial sense of politics knows, of course, authority is always much easier to possess in theory than to exercise in practice, particularly when grantees view it as a transgression on their intellectual independence. Nonetheless, the fact that the job is sometimes difficult does not make it impossible, and CTEP has accepted the challenge with enthusiasm.

Dr. Salmon does not agree with our assessment of the extent to which cooperative groups have consistently addressed key questions in therapy in a timely manner. As he notes, the efforts of the Myeloma Committee within the Southwest Oncology Group have, in fact, attempted to utilize the predictions of the somatic mutation theory in protocol design; although one can raise substantive questions about the extent to which SWOG 8229/30 is an adequate test of the Goldie-Coldman hypothesis, it is certainly a serious attempt to cope with the implications of the theory. There are a few other attempts in the group program to do this (and several more in gestation now). On the other hand, the FOMi/CAP (5-fluorouracil, vincristine, and mitomycin/cyclophosphamide, doxorubicin, and cisplatin) alternating study (SWOG 8012) cited by Dr. Salmon does not seem to have been formulated with the intent of testing the Goldie-Coldman hypothesis at all; the original protocol document contains nothing about the somatic mutation theory in the Objectives, Background, or References. Rather, SWOG 8012 appears to be based on the same set of empirical considerations that motivated many trials utilizing alternating combinations in the 1970s. There is nothing the matter with this, but the study simply cannot be represented as a prospective test of the Goldie-Coldman hypothesis. We continue to think that this hypothesis, addressing as it does a dominant cause of treatment failure in tumors initially sensitive to chemotherapy, has been grossly underutilized by investigators in the planning of specific clinical trials.

We certainly agree with Dr. Salmon that the Editorial is not itself a "mandate for change." CTEP has been involved in an ongoing dialogue with clinical investigators, the chairmen of the cooperative groups, and the DCT's BSC about the need for changes in the cooperative group program. At its last meeting, the BSC appointed a subcommittee to work with CTEP and the extramural oncology community in this effort. There currently exists a very large degree of agreement about the nature of the problems we face, and most of those involved in the process are optimistic that continued discussion will shortly yield a set of mutually acceptable solutions.

Dr. Crawford is certainly correct that the rapid entry of 600 patients with metastatic prostate cancer onto the intergroup trial has made the accrual phase of this study a great success. This experience shows, in fact, one of the great strengths of the existing group program—the capacity for rapid accrual to studies of high interest without the need to create new clinical trials organization for each new study. On the other hand, the rapid completion of accrual should not erase the memory of a very difficult and inefficient organizational phase. The lesson is that the planning of all priority trials must be streamlined; if a question is worth asking, then the sooner it is asked and answered, the better. As we have also noted, the adoption of common guidelines for intergroup studies and of common response and toxicity criteria would do much to facilitate the organization of future intergroup efforts.

Dr. Higby points out the importance of cost sharing in the support of clinical trials. We are well aware that NCI does not pay the full cost of cooperative group activities. Since the clinical trials budget is likely to remain relatively flat over the near future, we anticipate that the need for substantial cost sharing will remain. In the past, institutions have agreed to do this for a variety of reasons, including sympathy with the goals of clinical research, the desire to keep their medical staffs happy, and the perception that a relatively modest investment of this kind would lead to an advan-

tageous position in the increasingly competitive world of the "health care provider." As hospitals attempt to contain costs and as prospective payment expands and realizes its full impact, administrators may or may not continue to view participation in clinical research as worthwhile. If they do not, and if funding agencies like the NCI are called upon to pay a substantially larger proportion of research costs than they now do, the whole enterprise will be gravely threatened without a large infusion of new support.

Dr. Higby asserts that community physicians are increasingly alienated from the clinical trials effort and he exhorts the NCI to remedy the crisis in patient acquisition to trials. As everyone knows, of course, the NCI has been actively supporting community participation for years. The Cooperative Group Outreach Program and the Community Clinical Oncology Program (CCOP) are both attempts to increase the involvement of community physicians and patients in clinical trials. These programs contribute a very significant fraction of the total accrual to cooperative group trials, and it is clear that the whole cooperative group program would be vastly weaker without community participation. We agree with Dr. Higby's implication that more support would translate into increased physician participation and increased patient accrual, and if funds were available, we would like to see the cooperative group-community network expanded to two to three times its present size. We see no evidence for alienation and expect the RFA (Request for Application) for the CCOP recompetition to be hotly contested. We applaud those physicians who participate in trials on an unfunded basis. We do not agree with Dr. Higby that these individuals lack incentive; it seems clear that the desire to participate in clinical research and help answer important questions in therapy is itself a potent incentive. This is not to praise poverty or accept the current funding crunch as inevitable, but we do not see widespread alienation either.

The Letter by Pater et al raises many interesting issues. The distinction between explanatory and pragmatic goals in treatment trials is a useful one, and we also recognize that these goals may sometimes conflict. We take the view that the purpose of the clinical trials program is to answer reliably and quickly the most important questions in therapy. It seems to us that studies designed with important hypotheses in mind are more likely to address important questions than those designed without such an underpinning. We certainly do not expect, and have never asserted, that "improvements in cooperative group organization will resolve a difficulty that is fundamental to the nature of clinical research."

The National Cancer Institute of Canada's (NCIC) experience with several of its studies, as described by Pater et al, re-emphasizes the importance of timeliness; we must answer a research question before the community loses interest in it. As Pater et al note in their discussion of dose and dose intensity, the way in which one generates hypotheses and formulates specific questions may change with time. This is, of course, also true in laboratory investigation and would seem to be an inherent feature of science itself. Admittedly, the long duration and other peculiar features of clinical trials make it an especially awkward fact of life in this context. These realities do not, however, absolve us of the responsibility of doing the best we can on the basis of current understanding. Experimentation of any kind generally raises more questions than it answers and motivates further experimentation.

The discussion of NCIC's small cell lung cancer study by Pater et al is unclear. Either the cisplatin/etoposide combination is equal in activity and non-cross-resistant to CAV (cyclophosphamide, doxorubicin, and vincristine), or it is not. If it is, then one cannot invoke the superiority of cisplatin and etoposide to explain the results of the trial. If it is not, and one of the combinations is in fact significantly superior to the other, then the requirements of the somatic mutation theory have not been fulfilled by this trial design. In any case, the fact that trials in humans cannot address scientific hypotheses as unambiguously as animal experiments can is certainly true and will not surprise anyone.

Finally, Pater et al appear to confuse our enthusiasm for larger trials with the recommendations of Peto and his associates for very large and very simple studies involving perhaps tens of thousands of patients and concentrating on simple endpoints (eg, survival) with minimal need for monitoring and data collection. Although this approach may certainly be applicable to some settings (eg, a comparison of tamoxifen administration for different durations as an adjuvant to surgery in breast cancer), we don't think it applies to most kinds of pertinent research questions in oncology. Most therapies that seem worth testing now or are likely to come along any time soon will probably involve a degree of complexity and/or intensity that make substantial patient monitoring and attention to subsidiary endpoints essential. We were simply attempting to emphasize that trials should be substantially larger than many have been in the past, in order to target moderate but still medically important differences in efficacy. Since a study's complexity and size are both major determinants of its cost and also of the probability that it will be successfully completed, both must be carefully considered at the outset. Fundamentally, however, they are independent issues.

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Chemosensitization of Lomustine by Misonidazole, Benznidazole, and RSU 1069

The phenomenon of chemosensitization by nitroimidazoles is of considerable current interest both experimentally and clinically (*see* reviews cited in ref 1). The original lead compound, the radiosensitizer misonidazole [1-(2-nitroimidazol-1-yl)-3-methoxy-2-propanol], was shown to increase the activity of certain cytotoxic agents against mouse tumors in vivo to a greater extent than in normal tissues, resulting in an improved therapeutic index. This has been observed most frequently with the nitrogen mustards melphalan and cyclophosphamide and the chloroethylnitrosourea lomustine [1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea]. Although chemosensitization has been demonstrated in mice under conditions which closely mimic the exposures to misonidazole in man, and clinical trials have begun (1), the dose-limiting neurotoxicity of misonidazole has prompted the search for alternative sensitizers with greater effectiveness.

Two approaches have yielded promising results so far. Adams and co-workers (2) have shown potent chemosensitization of tumor response to melphalan and other agents with the compound RSU 1069 [1-(2-nitroimidazol-1-yl)-3-aziridino-2-propanol] in mice. This is a "mixed-function" sensitizer because it contains both a nitro and an aziridine (alkylating) group. More recently, Siemann and co-workers (1) have shown that similarly potent chemosensitization can be obtained for RSU 1069 with lomustine in mice.

The second approach results from studies which identified sensitizer lipophilicity as an important parameter in chemosensitization, and from which benznidazole [*N*-benzyl-(2-nitroimidazolyl)acetamide] was selected as a promising candidate for combination with lomustine in the clinic (3).

To allow direct comparison of results for misonidazole and the two new analogues, table 1 summarizes the results obtained by three independent groups, each using the same tumor and syngeneic mouse host. Two important points are clearly apparent: (*a*) At the doses used, the results obtained with the three sensitizers are similar, and the improvements in therapeutic gain over lomustine alone are very comparable. (*b*) With both benznidazole and RSU 1069, the same therapeutic advantage is obtained at a considerably lower dose than for misonidazole.

In an otherwise excellent paper by Siemann et al (1), the brief discussion of benznidazole may give rise to an inaccurate impression of its merits compared to RSU 1069 and misonidazole. Paragraph two states that benznidazole either "led to significantly increased normal tissue damage and consequently no therapeutic benefit or a gain equivalent to that obtained with larger misonidazole doses." Table 1 supports the latter result with 0.3 mmols/kg, a dose which results in a peak plasma level of 0.12 mM. A lack of therapeutic gain was seen by Hirst et al (10), but only with the much higher dose of 2 mmols/kg or with a multiple-injection schedule producing blood levels of 0.3–0.5 mM at the time of lomustine administration.

Two other important points are not mentioned in the discussion by Siemann et al (1). First, we should consider the equiactive doses of the three sensitizers as a proportion of their single-dose acute LD50 in mice (values from this laboratory): 0.3 mmols/kg of benznidazole is almost 30 times below the LD50 (8.3 mmols/kg) compared to about one- to two-thirds the LD50 for 2.5–5 mmols/kg of misonidazole (LD50, 8.5 mmols/kg) and 0.38 mmols/kg of RSU 1069 (LD50, 0.63 mmols/kg). Second, we should consider whether or not the concentrations of the new sensitizers shown to be required in mice can also be

TABLE 1.—Dose-modifying factors for chemosensitization of the response of tumor and normal tissues to lomustine by single doses of nitroimidazoles in C3H/He mice

Sensitizer (mmols/kg)	Investigating group (ref No.)†	Dose-modifying factor*			
		Tumor‡ (KHT sarcoma)	Peripheral wbcs§	Bone marrow (CFU-S)	Lethality¶ (LD50)
Misonidazole (2.5–5.0)	A (1,4–6)	1.8–2.4	1.0		1.2–1.4
	B (7,8)	1.5	1.0		1.1
	C (9,10)	1.5–1.9		1.0–1.5	
Benznidazole (0.3)	A (6)	2.0			1.3–1.4
	B (11)	1.5–2.0	1.2		1.3
RSU 1069 (0.38)	A (1)	1.9	1.0		1.0–1.2

*Isoeffect dose for lomustine alone/isoeffect dose for lomustine plus chemosensitizer. Results are for single doses of sensitizer and lomustine. Drugs were given ip, either simultaneously or with the sensitizer given 30–60 mins before lomustine.

†A = Rochester, NY, B = Cambridge, England, and C = Stanford, CA.

‡Regrowth delay or clonogenic survival.

§Day 3 (nadir).

¶30 days.

achieved safely in man. With 0.38 mmols/kg of RSU 1069 in mice, the peak plasma level is about 0.26 mM and the area under the curve (AUC) is about 0.18 mM.hr (12). At the maximum dose achievable in man (80 mg/m^2 or 0.38 mmols/m^2, the dose-limiting toxicity being acute gastrointestinal), the peak plasma concentration is about 0.024 mM and the AUC is about 0.03 mM.hr (A. Horwich, personal communication), which are lower exposures than those required in mice. However, analogues are under development which are at least five times less toxic than RSU 1069 (2) and these may allow potentially active concentrations to be achieved in man. With 0.3 mmols/kg of benznidazole in mice, the peak plasma concentration is 0.12 mM and the AUC is 0.35 mM.hr (13). These were readily achieved in a phase I study of benznidazole plus lomustine; moreover there was no toxicity associated with the benznidazole and no enhancement of the acute gastrointestinal or hematological toxicity of the nitrosourea (14). Following these promising results, a local phase II study of benznidazole and lomustine in malignant melanoma has been completed in Cambridge (15) and a national Medical Research Council phase III study in recurrent glioma is now in progress.

In conclusion, the evidence indicates that benznidazole is, compared to misonidazole, a considerably more potent chemosensitizer of lomustine tumor response in mice, and that active concentrations are attainable in man without increasing normal tissue toxicity; it is therefore worthy of further clinical evaluation. It is hoped that less toxic derivatives of RSU 1069 will also give rise to active exposures in the clinic. A strong case can be made for pursuing both avenues, since the mechanisms of action of the two sensitizers are unlikely to be identical. Thus, while both contain the nitro group and therefore may exert a proportion of their activity through bioreductive activation in hypoxic tumor cells (*see* reviews cited in ref 1), benznidazole is also able to modify the pharmacokinetics of lomustine (15), while RSU 1069 may exhibit DNA targeting through the monofunctional aziridine group.

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February 24, 1986

Linear and Exponential Interpolation

It has become common to cite point estimates for the median survival time, $\hat{m}$, in medical follow-up studies. There have been several methods for estimating the median by nonparametric approach. The best of them would be linear interpolation

$$\hat{m} = t + \frac{\hat{P}(t) - \frac{1}{2}}{\hat{P}(t) - \hat{P}(t')} (t' - t), \qquad [1]$$

which was proposed by Simon and Lee (1), where t is the largest survival time such that $\hat{P}(t) \geq \frac{1}{2}$ and t′ is the shortest survival time such that $\hat{P}(t') < \frac{1}{2}$. Since the product-limit survival estimator (2) is a step function, the median is generally not unambiguously defined.

However, equation [1] may not hold exactly, because no survival distribution is linear. A bias towards overestimating the median occurs if the true survival curve

is exponential, especially if $\hat{P}(t)$ and $\hat{P}(t')$ are far from $\frac{1}{2}$. The bias would probably increase when the data are analyzed by the Berkson-Gage procedure (3).

Since the exponential distribution plays a central role among survival distributions (4), it would be better to estimate the median using the exponential interpolation

$$\hat{m} = t + \frac{\log \hat{P}(t) - \log \frac{1}{2}}{\log \hat{P}(t) - \log \hat{P}(t')} (t' - t). \quad [2]$$

The $\hat{m}$ value from equation [2] is less than that from equation [1] and the bias is corrected. For data grouped by time interval, equation [2] becomes

$$\hat{m} = t_{k-1} + \frac{h_{k-1} (\log \hat{S}_{k-1} - \log \frac{1}{2})}{\log \hat{S}_{k-1} - \log \hat{S}_k}, \quad [3]$$

where the survival rate, $\frac{1}{2}$, lies between $\hat{S}_{k-1}$ and $\hat{S}_k$, the time interval of the group including $\hat{m}$ is $[t_{k-1}, t_k)$, and $h_{k-1} = |t_{k-1} - t_k|$. It is not much different from equation [2].

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April 18, 1986

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ANNOUNCEMENTS

Bone and Cancer: International Congress in Hanasaari

Helsinki, Finland, October 9–11, 1986

For further information, contact: European Forum for Orthopaedic Science Congress Bureau, PO Box 4, SF-00661 Helsinki, Finland.

Ninth Annual Bristol-Myers Symposium on Cancer Research

Washington, DC, October 15–16, 1986

The Vincent T. Lombardi Cancer Research Center of Georgetown University School of Medicine is organizing the Ninth Annual Bristol-Myers Symposium on Cancer Research. This year's topic will be "Mechanisms of Drug Resistance in Neoplastic Cells." Sessions include: general considerations of drug resistance; enzymatic basis of drug resistance; multidrug resistance; and the circumvention of resistance.

The annual Bristol-Myers symposium is part of an $8.34 million program of unrestricted grants for cancer research the company has sponsored since 1977 at 17 institutions in the United States, Canada, Europe, and Japan.

For more information, contact: Ms. Lillian Kamal, Administrator, Vincent T. Lombardi Cancer Research Center, Georgetown University School of Medicine, 3800 Reservoir Rd, NW, Washington, DC 20007.

Fifth NCI-EORTC Symposium on New Drugs in Cancer Therapy

Amsterdam, The Netherlands, October 22–24, 1986

This symposium will be organized by the European Organization for Research on Treatment of Cancer (EORTC) and by the National Cancer Institute (NCI), National Institutes of Health. The following topics will be discussed: screening and pharmacology, formulation, phase I trials and clinical pharmacology, phase II trials of new cytostatic agents, new analogs, and biological response modifiers.

For further information, contact: Symposium Secretariat, EORTC-New Drug Development Office, Department of Oncology, Free University Hospital, De Boelelaan 1117, NL-1081 HV Amsterdam, The Netherlands [telephone: (20) 548-5193, 548-5192].

Cincinnati Cancer Conference V: Breast Cancer

Cincinnati, Ohio, October 31–November 1, 1986

The Cincinnati Cancer Conference V: Breast Cancer is being sponsored by the Bethesda Hospital, Inc, the American Cancer Society, and the University of Cincinnati College of Medicine. The objectives are as follows: upon completion of the CME activity, physicians will be able to demonstrate ability to describe the role of various treatment modalities in breast cancer; discuss methods of detection of breast cancer; and apply the results of clinical research to patients with breast cancer.

Featured faculty are as follows: Gianni Bonadonna, Stephen K. Carter, Caldwell B. Esselstyn, Jr, Gilbert H. Fletcher, Jay R. Harris, John A. Katzenellenbogen, Marc E. Lippman, David P. Rose, Philip Strax, and Douglass C. Tormey.

For further information, contact: Tom O'Connor, Course Manager, Bethesda Hospital, Inc, 619 Oak St, Cincinnati, OH 45206 (telephone: 513-569-6389).

Chemotherapy Foundation Symposium VII—Innovative Cancer Chemotherapy for Tomorrow

New York, New York, November 12–14, 1986

The Sheraton Centre Hotel in New York City will be the location for the Chemotherapy Foundation Symposium VII—Innovative Cancer Chemotherapy for Tomorrow, to be held November 12–14, 1986. Individual sessions will be devoted to postmenopausal breast cancer polychemotherapy, differentiation chemotherapy, chemoimmunotherapy, and new phase II drugs.

The 3-day symposium is being sponsored by the Division of Medical Oncology, Department of Medicine, Department of Neoplastic Diseases, and the Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine (CUNY).

For further information, contact: Director, The Page and William Black Post-Graduate School of Medicine, One Gustave L. Levy Place, New York, NY 10029 (telephone: 212-650-6772).

AIDS and the Nervous System

San Francisco, California, December 11–12, 1986

This symposium, located in the St. Francis Hotel and sponsored by the University of California in San Francisco, is designed to present the most recent information on the care of AIDS patients with neurological disease including: overview and neuroepidemiology, clinical syndromes and diagnosis, primary and opportunistic viral infections, nonviral infectious disease, Kaposi's sarcoma and systemic lymphomas, patient care issues, and recent research developments. Ten hours of ACCME/AMA/CMA Category 1 credit may be earned by attending the symposium.

For further information, contact: Extended Programs in Medical Education, Rm 569-U, University of California, San Francisco, CA 94143 (telephone: 415-476-4251).

International Symposium on Breast Cancer

New Delhi, India, January 1–4, 1987

The Tata Memorial Center, Bombay, and association of Surgeons of India are jointly sponsoring an International Symposium on Breast Cancer to be held from January 1–4, 1987, at the Taj Palace Hotel, New Delhi, India. The symposium will address the current state of the art in all aspects of breast cancer including basic research that is of interest to the clinician.

For further information, contact: Dr. I. Mittra, Organising Secretary, Ernest Borges Marg, Parel, Bombay 400012, India.

Major Advances in Oncology 1986–1987: Focus on Melanoma

Cleveland, Ohio, January 31, 1987

The R. Livingston Ireland Cancer Center of University Hospitals of Cleveland will be presenting this conference for physicians. Topics will include the following: confusion about dysplasia, dysplastic cells, dysplastic nevi, and the dysplastic nevus syndrome; and the biology of melanoma. Other topics are to be presented by faculty from the Case Western Reserve University School of Medicine.

All conferences carry CME credit.

For further information, contact: Barbara Guy, Assistant to the Director, Ireland Cancer Center, Lowman Bldg-211, University Hospitals of Cleveland, 2074 Abington Rd, Cleveland, OH 44106 (telephone: 216-844-7856).

5th International Conference on the Adjuvant Therapy of Cancer

Tucson, Arizona, March 11–14, 1987

The 5th International Conference on the Adjuvant Therapy of Cancer will be held at the Tucson Convention Center, Wednesday, March 11, through Saturday, March 14, 1987. The Arizona Cancer Center is sponsoring this conference. Sydney E. Salmon will serve as conference chairman. The scientific advisory committee members are Vincent DeVita, Jr, Bernard Fisher, Emil Frei, III, and Stephen E. Jones.

The deadline for submission of abstracts (prepared in the format of AACR/ASCO) is *December 1, 1986.*

For further information, contact: Mary Humphrey, Conference Coordinator, Arizona Cancer Center, The University of Arizona College of Medicine, Tucson, AZ 85724 (telephone: 602-626-6044).

Major Advances in Oncology 1986–1987: New Strategies in the Management of Lung Cancer

Cleveland, Ohio, April 25, 1987

The R. Livingston Ireland Cancer Center of University Hospitals of Cleveland will be presenting this conference for physicians. Topics will include the following: drug resistance in human tumors: recent developments in new therapeutic approaches; management of non-small cell cancer; and small cell lung cancer: overcoming an impasse. Other topics will be presented by faculty from the Case Western Reserve University School of Medicine.

All conferences carry CME credit.

For further information, contact: Barbara Guy, Assistant to the Director, Ireland Cancer Center, Lowman Bldg-211, University Hospitals of Cleveland, 2074 Abington Rd, Cleveland, OH 44106 (telephone: 216-844-7856).

First International Symposium on Organ Directed Toxicities of Anticancer Drugs

Burlington, Vermont, June 4–6, 1987

The First International Symposium on Organ Directed Toxicities of Anticancer Drugs will be held in Burlington, VT, June 4–6, 1987. The purpose is to address new developments with biological, chemical, pharmacological, and immunological components of the organ specific toxicities of clinically important anticancer drugs.

Day 1 will be devoted to mechanisms of anthracycline-induced cardiotoxicity; Day 2 will feature the mechanisms of bleomycin-induced pulmonary fibrosis; and Day 3 will focus on the mechanisms of platinum-induced nephrotoxicity. Each session will include presentations by five invited speakers, the viewing of scientific posters, and open discussion.

For further information, contact: Miles P. Hacker, PhD, Vermont Regional Cancer Center, One South Prospect St, Burlington, VT 05401 (telephone: 802-656-4414).

Third International Conference on Malignant Lymphoma: Current Status and Prospects

Lugano, Switzerland, June 10–13, 1987

The Palazzo dei Congressi is the location for this series of lectures and workshops dealing with the diagnosis and treatment of Hodgkin's and non-Hodgkin's lymphoma in adults and children. Most lectures will be given by invited speakers. The program will include free presentations, workshops, and a poster session. The deadline for the receipt of abstracts is *January 15, 1987.*

For further information, contact: F. Cavalli, MD, Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland (telephone: 091-23-62-10).

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New *NCI Monographs*

Meetings previously published under the titles *Cancer Treatment Symposia* and the *National Cancer Institute Monograph Series* will be presented under one title, *NCI Monographs.* The monographs will be soft bound and numbered sequentially as they appear.

Material presented in the new version of the monographs will, on an alternating basis, reflect meetings and reports accepted and reviewed by either the *Cancer Treatment Reports* or the *Journal of the National Cancer Institute* Editorial Boards.

The first issue of *NCI Monographs* is the "Proceedings of the NIH Consensus Development Conference on Adjuvant Chemotherapy and Endocrine Therapy for Breast Cancer" (see advertisement on next page).

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EDITORIALS

1051 Low-Grade Non-Hodgkin's Lymphomas Revisited

1055 Follicular Lymphoma—Do No Harm

ORIGINAL ARTICLES

1059 Pharmacology and Toxicity of High-Dose Cytarabine by 72-Hour Continuous Infusion

1067 Effects of Exercise on Bleomycin-Induced Pulmonary Toxicity in Mice

1073 Ineffectiveness of Levamisole in Prolonging Remission or Survival of Women Treated With Cyclophosphamide, Doxorubicin, and 5-Fluorouracil for Good-Risk Metastatic Breast Carcinoma: A Southeastern Cancer Study Group Trial

1081 Hyponatremia and Other Toxic Effects During a Phase I Trial of Recombinant Human Gamma Interferon and Vinblastine

1085 Randomized Comparisons of Radiotherapy and Carmustine Versus Procarbazine Versus Dacarbazine for the Treatment of Malignant Gliomas Following Surgery: A Southwest Oncology Group Study

1091 Trial of the Combination of Mitomycin, Vindesine, and Cisplatin in Patients With Advanced Non-Small Cell Lung Cancer

1097 Phase II Trials of Cisplatin and Piperazinedione as Single Agents in the Treatment of Advanced or Recurrent Non-Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study

1101 Extensive Non-Small Cell Lung Cancer Treated With Mitomycin, Cisplatin, and Vindesine (MiPE): A Southwest Oncology Group Study

REVIEW ARTICLES

1105 Therapeutic Response in Phase I Trials of Antineoplastic Agents

1117 Association of Severe and Fatal Infections and Treatment With Pentostatin

BRIEF REPORTS

1121 Treatment of Kaposi's Sarcoma in Acquired Immunodeficiency Syndrome With an Alternating Vincristine-Vinblastine Regimen

CLINICAL TRIALS SUMMARIES

1123 Phase II Study of Fludarabine Phosphate for the Treatment of Advanced Non-Small Cell Carcinoma of the Lung: A Southwest Oncology Group Study

1125 Phase II Trial of Mitoxantrone in Advanced Primary Liver Cancer: A Cancer and Leukemia Group B Study

1127 Phase II Clinical Trial of Diaziquone in the Treatment of Patients With Recurrent Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study

1129 Phase II Study of Spirogermanium in Metastatic Prostate Cancer

LETTERS

1131 "Some Thoughts on the Future of Clinical Trials in Cancer"

1133 "Some Thoughts on the Future of Clinical Trials in Cancer"

1133 Testing Hypotheses in Clinical Trials: Experience of the National Cancer Institute of Canada Clinical Trials Group

1136 "Some Thoughts on the Future of Clinical Trials in Cancer"

1137 *Reply:* Clinical Trials

1139 Chemosensitization of Lomustine by Misonidazole, Benznidazole, and RSU 1069

1140 Linear and Exponential Interpolation

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September 1986